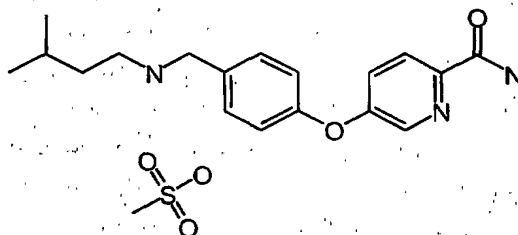


**Example 389**

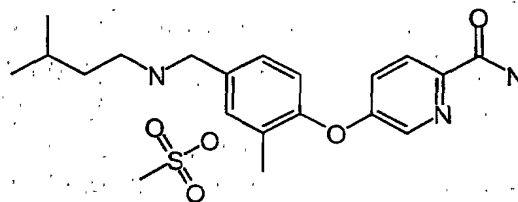
5-{4-[(3-Methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide methanesulfonate



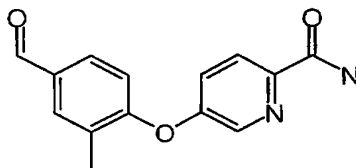
Suspend 5-(4-formylphenoxy)pyridine-2-carboxamide (0.0429 g, 0.160 mmol) in methanol (1.5 mL). Add isoamylamine (0.0185 mL, 0.112 mmol) and 3 Å molecular sieves. Stir at room temperature overnight. Add NaBH<sub>4</sub> (in small excess) and stir for additional 3 hours before filtering. Add saturated aqueous NaHCO<sub>3</sub> (20 mL) to the filtrate. Extract with dichloromethane (3 x 50 mL). Dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. Purify by flash chromatography, eluting with 5% (2.0 M NH<sub>3</sub> in methanol), 70% ethyl acetate and 25% hexanes to give the title compound as a free base (0.0323 g). Redissolve the product in THF (1 mL) and add a solution of 1.27 M methanesulfonate in THF (0.0298 mL) to give the title compound (0.039 g, 64.6%): MS ES<sup>+</sup> 314.0 (M+H)<sup>+</sup>, base peak MS ES<sup>+</sup> 226.9 (M-NHCH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)<sup>+</sup>; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 9.3 min, 96.0% purity.

**Example 390**

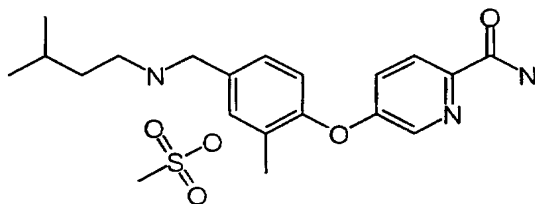
5-{2-Methyl-4-[(3-methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide methanesulfonate



## Part A: 5-(4-Formyl-2-methylphenoxy)pyridine-2-carboxamide



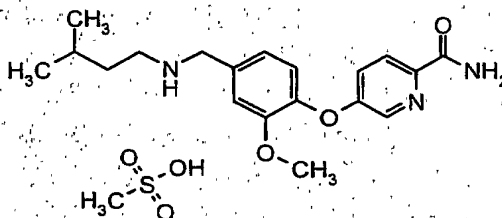
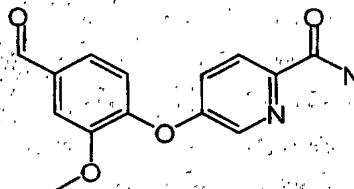
Using a method similar to Example 388 Part D, using 5-fluoropyridine-2-carboxamide (Example 388 Part C) (0.400 g, 2.85 mmol) and 4-[1,3]dioxolan-2-yl-2-methylphenol (Example 388, Part C2) (0.514 g, 2.85 mmol) gives the title compound (0.259 g): TLC [silica gel 60 F<sub>254</sub>, 30% ethyl acetate in dichloromethane] R<sub>f</sub> = 0.20; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 12.1 min, 73.1% purity.

Part B: 5-{2-Methyl-4-[(3-methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide  
methanesulfonate

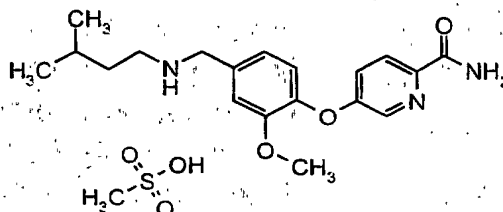
Using a method similar to Example 389, using 5-(4-formyl-2-methylphenoxy)pyridine-2-carboxamide (0.0429 g, 0.160 mmol) and isoamylamine (0.018 mL, 0.160 mmol) gives the title compound (0.0576 g, 92.1%): TOF MS ES<sup>+</sup> 328.2 (M+H)<sup>+</sup>, base peak MS ES<sup>+</sup> 241.1 (M-NHCH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub> 328.2025 (M+H)<sup>+</sup>, found 328.2015, time 0.33 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 9.9 min, 100% purity.

**Example 391**

5-{2-Methoxy-4-[(3-methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide  
methanesulfonate

**Part A: 5-(4-Formyl-2-methoxyphenoxy)pyridine-2-carboxamide**

Using a method similar to Example 388 Part D, using 5-fluoropyridine-2-carboxamide (Example 388 Part C) (0.400 g, 2.85 mmol) and 4-[1,3]dioxolan-2-yl-2-methoxyphenol (Example 386, Part C2) (0.560 g, 2.85 mmol) gives the title compound (0.126 g, 16%): MS ES<sup>+</sup> 272.9 (M+H)<sup>+</sup>; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 11.1 min, 97.2% purity.

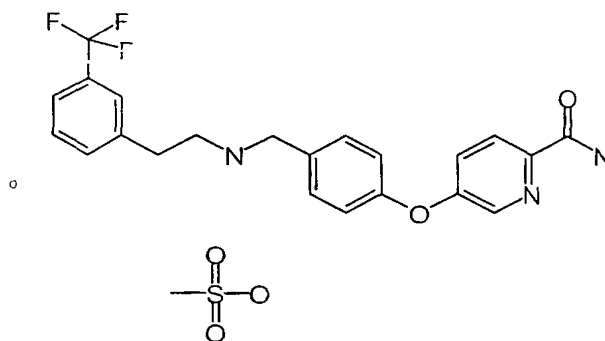
**Part B: 5-{2-Methoxy-4-[(3-methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide methanesulfonate**

Using a method similar to Example 389, using 5-(4-formyl-2-methoxyphenoxy)pyridine-2-carboxamide (0.043 g, 0.160 mmol) and isoamylamine (0.018 mL, 0.160 mmol) gives the title compound (0.055 g, 81.2%): TOF MS ES<sup>+</sup> 344.2

(M+H)<sup>+</sup>, base peak MS ES<sup>+</sup> 257.1 (M-NHCH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub> 344.1974 (M+H)<sup>+</sup>, found 344.1978, time 0.35 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 9.5 min, 97.0% purity.

### Example 392

5-(4-{[2-(3-Trifluoromethylphenyl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide  
methanesulfonate

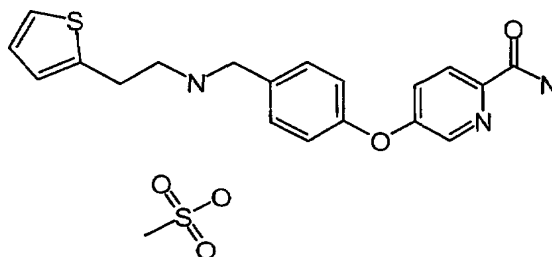


Using a method similar to Example 389, using 5-(4-formylphenoxy)pyridine-2-carboxamide (Example 388, Part D) (0.0337 g, 0.139 mmol) and 2-(3-trifluoromethylphenyl)ethylamine (0.0263 g, 0.139 mmol) gives the title compound (0.0127 g, 18%): MS ES<sup>+</sup> 415.9 (M+H)<sup>+</sup>, base peak MS ES<sup>+</sup> 226.9 (M-NHCH<sub>2</sub>CH<sub>2</sub>CH(C<sub>6</sub>H<sub>4</sub>)CF<sub>3</sub>)<sup>+</sup>; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 11.4 min, 100% purity.



**Example 393**

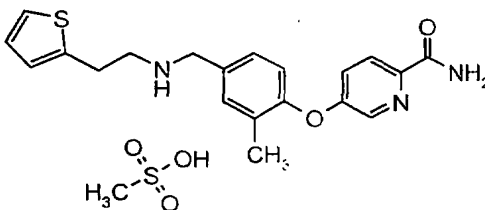
5-{4-[(2-Thiophen-2-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide  
methanesulfonate



Using a method similar to Example 389, using 5-(4-formylphenoxy)pyridine-2-carboxamide (Example 388, Part D) (0.033 g, 0.136 mmol) and 2-(2-thienyl)ethylamine (0.0208 g, 0.163 mmol) gives the title compound (0.039 g, 64%): TOF MS  $ES^+$  354.1 ( $M+H$ ) $^+$ , base peak MS  $ES^+$  227.1 ( $M-NHCH_2CH_2(C_4H_3S)$ ) $^+$ , HRMS calcd for  $C_{19}H_{20}N_3O_2S$  354.1276 ( $M+H$ ) $^+$ , found 354.1298, time 0.30 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min],  $t_R$  = 9.5 min, 98.4% purity.

**Example 394**

5-{2-Methyl-4-[(2-thiophen-2-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide  
methanesulfonate

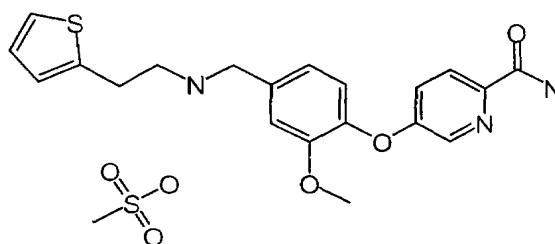


Using a method similar to Example 389, a reaction of 5-(4-formyl-2-methylphenoxy)pyridine-2-carboxamide (Example 390, Part A) (0.0349 g, 0.136 mmol) and 2-(2-thienyl)ethylamine (0.021 mL, 0.163 mmol) gives the title compound (0.0462 g, 73%): TOF MS  $ES^+$  368.1 ( $M+H$ ) $^+$ , base peak MS  $ES^+$  241.1 ( $M-NHCH_2CH_2(C_4H_3S)$ ) $^+$ , HRMS calcd for  $C_{20}H_{22}N_3O_2S$  368.1433 ( $M+H$ ) $^+$ , found 368.1436, time 0.36 min; HPLC

[YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min],  $t_R$  = 10.0 min, 100% purity.

### Example 395

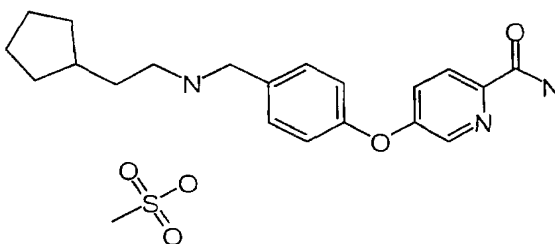
5-{2-Methoxy-4-[(2-thiophen-2-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide methanesulfonate



Using a method similar to Example 389, using 5-(4-formyl-2-methoxyphenoxy)pyridine-2-carboxamide (Example 391, Part A) (0.0370 g, 0.136 mmol) and 2-(2-thienyl)ethylamine (0.021 mL, 0.163 mmol) gives the title compound (0.025 g, 38%): TOF MS  $ES^+$  384.1 ( $M+H$ ) $^+$ , base peak MS  $ES^+$  257.1 ( $M-NHCH_2CH_2(C_4H_3S)$ ) $^+$ , HRMS calcd for  $C_{20}H_{22}N_3O_3S$  384.1382 ( $M+H$ ) $^+$ , found 384.1373, time 0.37 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min],  $t_R$  = 9.6 min, 100% purity.

### Example 396

5-{4-[(2-Cyclopentylethylamino)methyl]phenoxy}pyridine-2-carboxamide methanesulfonate

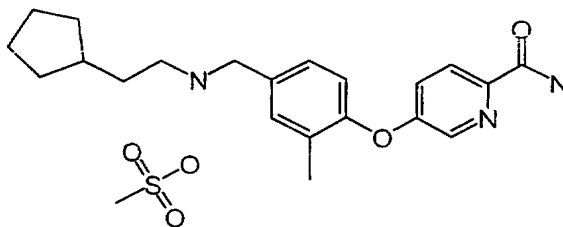


Using a method similar to Example 389, and using 5-(4-formylphenoxy)pyridine-2-carboxamide (Example 388, Part D) (0.033 g, 0.138 mmol) and 2-cyclopentylethylamine (0.0156 g, 0.138 mmol) gives the title compound (0.0308 g, 51%):

TOF MS ES<sup>+</sup> 340.2 (M+H)<sup>+</sup>, base peak MS ES<sup>+</sup> 227.1 (M-NHCH<sub>2</sub>CH<sub>2</sub>(C<sub>5</sub>H<sub>9</sub>))<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub> 340.2025 (M+H)<sup>+</sup>, found 340.2039, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 7.8 min, 95.9% purity.

### Example 397

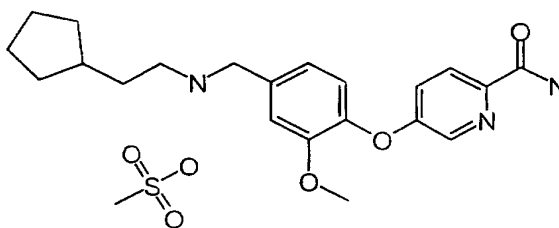
5-{4-[(2-Cyclopentylethylamino)methyl]-2-methylphenoxy}pyridine-2-carboxamide  
methanesulfonate



Using a method similar to Example 389, a reaction of 5-(4-formyl-2-methylphenoxy)pyridine-2-carboxamide (Example 390, Part A) (0.0353 g, 0.138 mmol) and 2-cyclopentylethylamine (0.0156 g, 0.138 mmol) gives the title compound (0.0349 g, 56.3%): TOF MS ES<sup>+</sup> 354.2 (M+H)<sup>+</sup>, base peak MS ES<sup>+</sup> 241.1 (M-NHCH<sub>2</sub>CH<sub>2</sub>(C<sub>5</sub>H<sub>9</sub>))<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>2</sub> 354.2182 (M+H)<sup>+</sup>, found 354.2188, time 0.38 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 8.5 min, 96.0% purity.

### Example 398

5-{4-[(2-Cyclopentylethylamino)methyl]-2-methoxyphenoxy}pyridine-2-carboxamide  
methanesulfonate

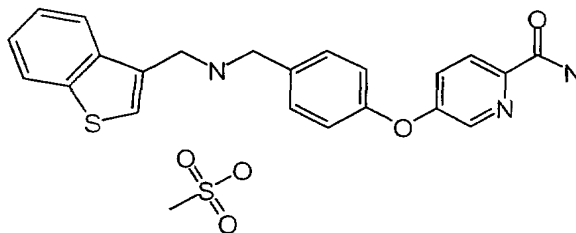


Using a method similar to Example 389, a reaction of 5-(4-formyl-2-methoxyphenoxy)pyridine-2-carboxamide (Example 391, Part A) (0.0375 g, 0.138 mmol)

and 2-cyclopentylethylamine (0.0156 g, 0.138 mmol) gives the title compound (0.034 g, 52.9%): TOF MS ES<sup>+</sup> 370.2 (M+H)<sup>+</sup>, base peak MS ES<sup>+</sup> 257.1 (M-NHCH<sub>2</sub>CH<sub>2</sub>(C<sub>5</sub>H<sub>9</sub>))<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>3</sub> 370.2123 (M+H)<sup>+</sup>, found 370.2155, time 0.38 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 10.5 min, 96.1% purity.

### Example 399

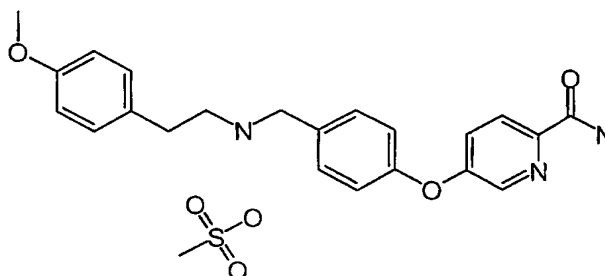
5-(4- {[(Benzo[*b*]thiophen-3-ylmethyl)amino]methyl}phenoxy)pyridine-2-carboxamide  
methanesulfonate



Using a method similar to Example 389, a reaction of 5-(4-formylphenoxy)pyridine-2-carboxamide (Example 388, Part D) (0.037 g, 0.154 mmol) and benzo[*b*]thiophen-3-ylmethylamine (from the hydrochloride salt freed on a 1 g SCX column washing with methanol and eluting with 2.0 M NH<sub>3</sub> in methanol) (0.0485 g, 0.297 mmol) gives the title compound (0.0398 g, 53%): TOF MS ES<sup>+</sup>:TIC, 390.1 (M+H)<sup>+</sup>, HRMS calcd for C<sub>22</sub>H<sub>20</sub>N<sub>3</sub>O<sub>2</sub>S 390.1276 (M+H)<sup>+</sup>, found 390.1261, time 0.38 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 8.0 min, 100% purity; Anal. Calcd for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>S·1.5CH<sub>4</sub>O<sub>3</sub>S: C, 52.89; H, 4.72; N, 7.72. Found: C, 52.69; H, 4.56; N, 7.72.

**Example 400**

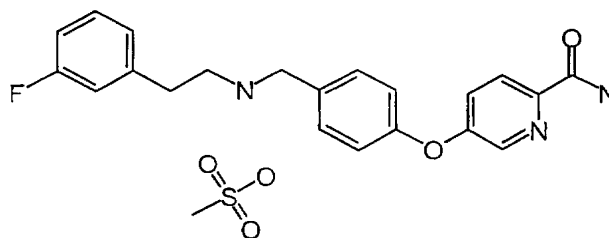
5-(4-{[2-(4-Methoxyphenyl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide  
methanesulfonate



Using a method similar to Example 389, a reaction of 5-(4-formylphenoxy)pyridine-2-carboxamide (Example 388, Part D) (0.039 g, 0.159 mmol) and 4-methoxyphenethylamine (0.023 mL, 0.159 mmol) gives the title compound (0.0241 g, 32%): TOF MS  $ES^+$  378.2 (M+H) $^+$ , HRMS calcd for  $C_{22}H_{24}N_3O_3$  378.1818 (M+H) $^+$ , found 378.1836, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  = 7.2 min, 100% purity; Anal. Calcd for  $C_{22}H_{23}N_3O_3 \cdot 1.1CH_4O_3S \cdot 0.4H_2O$ : C, 56.58; H, 5.80; N, 8.52. Found: C, 56.18; H, 5.67; N, 8.20.

**Example 401**

5-(4-{[2-(3-Fluorophenyl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide  
methanesulfonate

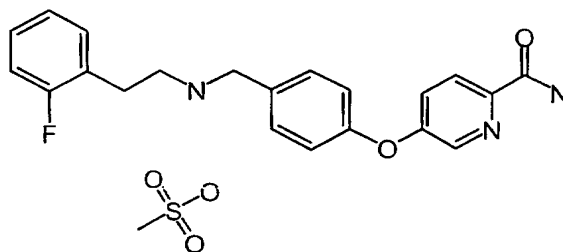


Using a method similar to Example 389, using 5-(4-formylphenoxy)pyridine-2-carboxamide (Example 388, Part D) (0.040 g, 0.164 mmol) and 3-fluorophenethylamine (0.024 mL, 0.181 mmol) gives the title compound (0.044 g, 58.1%): TOF MS  $ES^+$  366.2 (M+H) $^+$ , HRMS calcd for  $C_{21}H_{21}N_3O_2F$  366.1618 (M+H) $^+$ , found 366.1617, time 0.38

min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  = 7.5 min, 100% purity.

### Example 402

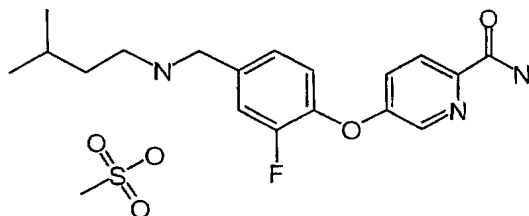
5-(4-{[2-(2-Fluorophenyl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide  
methanesulfonate



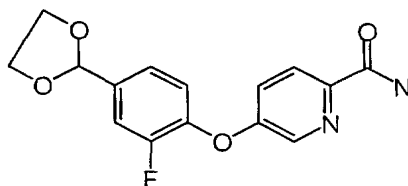
Using a method similar to Example 389, a reaction of 5-(4-formylphenoxy)pyridine-2-carboxamide (Example 388, Part D) (0.040 g, 0.164 mmol) and 2-fluorophenethylamine (0.024 mL, 0.181 mmol) gives the title compound (0.0324 g, 42.8%): TOF MS ES<sup>+</sup> 366.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>F 366.1618 (M+H)<sup>+</sup>, found 366.1623, time 0.38 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 7.3 min, 100% purity.

**Example 403**

5-{2-Fluoro-4-[(3-methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide  
methanesulfonate

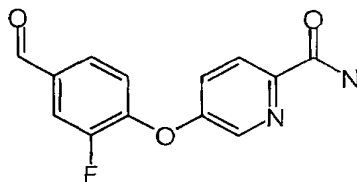


Part A: 5-(4-[1,3]Dioxolan-2-yl-2-fluorophenoxy)pyridine-2-carboxamide



Take up 4-[1,3]dioxolan-2-yl-2-fluorophenol (Example 388, Part C2) (0.400 g, 2.14 mmol), 5-fluoropyridine-2-carboxamide (Example 388, Part C) (0.299 g, 2.14 mmol) and  $K_2CO_3$  (0.514 g, 2.85 mmol) in DMF (5.3 mL). Heat at 100 °C overnight before concentrating to dryness. Take the black tar up in dichloromethane and filter through a silica gel plug. Wash the plug with ethyl acetate (3 x 150 mL). Concentrate the filtrate. Purify by flash chromatography, eluting with 30-35% ethyl acetate in dichloromethane until the 5-fluoropyridine-2-carboxamide elutes off the column. Then elute with 100% ethyl acetate to give the title compound (0.317 g, 48.8%): MS  $ES^+$  305.0 ( $M+H$ ) $^+$ ; TLC [silica gel 60 F<sub>254</sub>, 30% ethyl acetate in dichloromethane]  $R_f$  = 0.16.

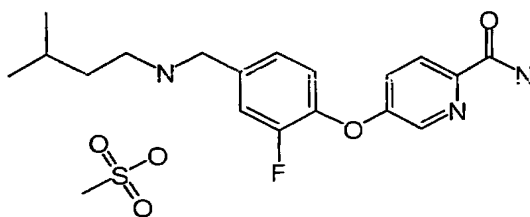
Part B: 5-(2-Fluoro-4-formylphenoxy)pyridine-2-carboxamide



Take up 5-(4-[1,3]dioxolan-2-yl-2-fluorophenoxy)pyridine-2-carboxamide (0.316 g, 1.04 mmol) in 88% formic acid (5.2 mL). Stir at room temperature for 1.25 hours before diluting with water. Extract with dichloromethane (2 x 50 mL). Wash the organic

layer with brine (1 x 25 mL), dry over  $\text{Na}_2\text{SO}_4$ , filter and concentrate to give the title compound (0.269 g, 99.6%): TOF MS  $\text{ES}^+$  261.1 ( $\text{M}+\text{H}^+$ ), HRMS calcd for  $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_3\text{F}$  261.0675 ( $\text{M}+\text{H}^+$ ), found 261.0682, time 0.37 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  9.0 min, 100% purity.

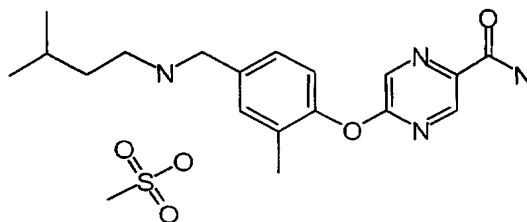
**Part C: 5-{2-Fluoro-4-[(3-methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide methanesulfonate**



Using a method similar to Example 389, using 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (0.0326 g, 0.125 mmol) and isoamylamine (0.0145 mL, 0.125 mmol) gives the title compound (0.0412 g, 69%): TOF MS  $\text{ES}^+$  332.2 ( $\text{M}+\text{H}^+$ ), HRMS calcd for  $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_2\text{F}$  332.1774 ( $\text{M}+\text{H}^+$ ), found 332.1787, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  = 6.7 min, 100% purity.

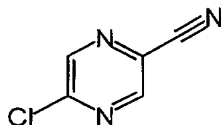
**Example 404**

**5-{2-Methyl-4-[(3-methylbutylamino)methyl]phenoxy}pyrazine-2-carboxamide methanesulfonate**



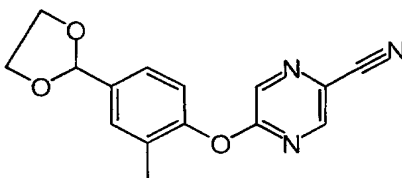


## Part A: 5-Chloropyrazine-2-carbonitrile



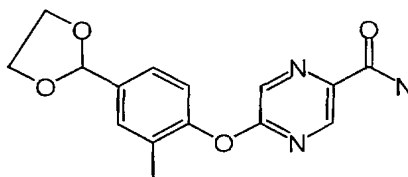
Dissolve 5-chloropyrazine-2-carboxamide (Example 389, Part A) (0.0878 g, 0.557 mmol) in POCl<sub>3</sub> (5.6 mL) and heat at reflux for 35 minutes. Concentrate the reaction mixture. Take up the dark oil in saturated aqueous NaHCO<sub>3</sub> (15 mL) and extract with dichloromethane (2 x 25 mL). Wash the organic layer with brine (1 x 15 mL), dry over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. Purify by flash chromatography, eluting with 10% ethyl acetate in hexanes to give the title compound (0.0498 g, 64.0%): GC/MS, MS ES<sup>+</sup> 139 (M)<sup>+</sup>, time 10.6 min, % of total 100%; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> 8.2 min, 100% purity.

## Part B: 5-(4-[1,3]dioxolan-2-yl-2-methylphenoxy)pyrazine-2-carbonitrile



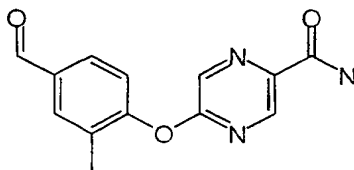
Take up 4-[1,3]dioxolan-2-yl-2-methylphenol (Example 388, Part C2) (0.288 g, 2.06 mmol), 5-chloropyrazine-2-carbonitrile (0.372 g, 2.06 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.428 g, 3.10 mmol) in DMF (13.8 mL). Heat at 100 °C for 45 minutes. Cool to 80 °C and stir overnight. Dilute the reaction mixture with dichloromethane (100 mL). Wash the organic layer with saturated aqueous NaHCO<sub>3</sub> (2 x 25 mL) and brine (1 x 25 mL). Dry over Na<sub>2</sub>CO<sub>3</sub>, filter and concentrate. Purify by flash chromatography, eluting with 30% ethyl acetate in hexanes to give the title compound (0.560 g, 95.58%): TLC [silica gel 60 F<sub>254</sub>, 30% ethyl acetate in hexanes] R<sub>f</sub> = 0.52.

## Part C: 5-(4-[1,3]Dioxolan-2-yl-2-methylphenoxy)pyrazine-2-carboxamide



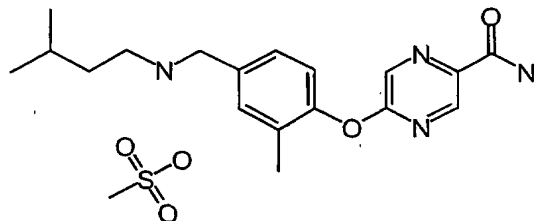
Take up 5-(4-[1,3]dioxolan-2-yl-2-methylphenoxy)pyrazine-2-carbonitrile (0.082 g, 0.305 mmol) and  $K_2CO_3$  (0.020 g, 0.152 mmol) in DMSO (3.0 mL). Add 30%  $H_2O_2$  (0.090 mL, 0.792 mmol) and stir at room temperature for 1.5 hours before quenching with water (10 mL). Extract with ethyl acetate (50 mL). Wash the organic layer with water (1 x 10 mL), dry over  $Na_2SO_4$ , filter and concentrate. Purify by flash chromatography, eluting with 40% ethyl acetate in dichloromethane to give the title compound (0.063 g, 68.6%): MS  $ES^+$  302.0 ( $M+H$ ) $^+$ ; TLC [silica gel 60 F<sub>254</sub>, 40% ethyl acetate in dichloromethane]  $R_f$  = 0.17.

## Part D: 5-(4-Formyl-2-methylphenoxy)pyrazine-2-carboxamide



Using a method similar to (Example 403, Part B), a reaction of 5-(4-[1,3]dioxolan-2-yl-2-methylphenoxy)pyrazine-2-carboxamide (0.055 g, 0.183 mmol) gives the title compound (0.047 g, 100%): HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  8.6 min, 100% purity; TLC [silica gel 60 F<sub>254</sub>, 30% ethyl acetate in dichloromethane]  $R_f$  = 0.22.

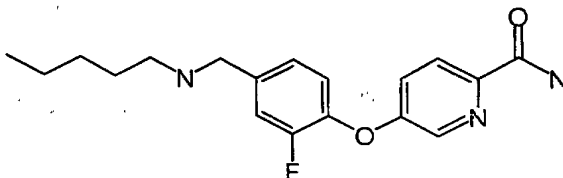
Part E: 5-{2-Methyl-4-[(3-methylbutylamino)methyl] phenoxy}pyrazine-2-carboxamide  
methanesulfonate



Using a method similar to Example 389, a reaction of 5-(4-formyl-2-methylphenoxy)pyrazine-2-carboxamide (0.0441 g, 0.171 mmol) and isoamylamine (0.020 mL, 0.171 mmol) gives the title compound (0.0563 g, 77.5%): TOF MS ES<sup>+</sup> 329.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>25</sub>N<sub>4</sub>O<sub>2</sub> 329.1978 (M+H)<sup>+</sup>, found 329.1985, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 6.4 min, 94.1% purity.

**Example 405**

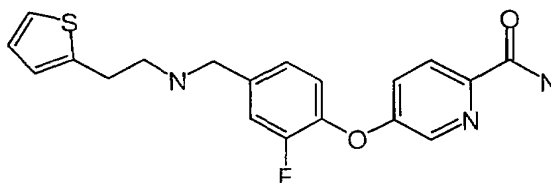
5-(2-Fluoro-4-pentylaminomethylphenoxy)pyridine-2-carboxamide



Place 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.040 g, 0.154 mmol), amylamine (0.0139 g, 0.154 mmol) and 3 Å molecular sieves in a vial. Add methanol (1.5 mL), cap and stir overnight. Add NaBH<sub>4</sub> (in excess over two portions) and stir until the gasses stop evolving. Load directly onto a 5 g SCX column. Wash with methanol (10 mL), then elute with 2.0 M NH<sub>3</sub> in methanol. Purify by loading the product onto a 5 g loading cartridge and eluting through a 10 g ISCO® column with 50% ethyl acetate, 5% (2.0 M NH<sub>3</sub> in methanol) and 45% hexanes to give the title compound (0.0387 g, 76.0%: TOF MS ES<sup>+</sup> 332.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>F 332.1774 (M+H)<sup>+</sup>, found 332.1765, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 6.9 min, 100% purity.

**Example 406**

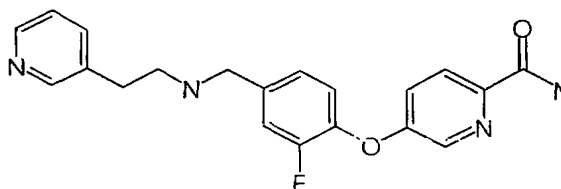
5-{2-Fluoro-4-[(2-thiophen-2-ylethylamino)methyl]phenoxy} pyridine-2-carboxamide



Using a method similar to Example 405, using 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.040 g, 0.154 mmol) and 2-(2-thienyl)ethylamine (0.0196 g, 0.154 mmol) gives the title compound (0.0344 g, 60.2%): TOF MS  $ES^+$  372.1 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{19}H_{19}N_3O_2FS$  372.1182 ( $M+H$ ) $^+$ , found 372.1168, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  = 6.9 min, 100% purity.

**Example 407**

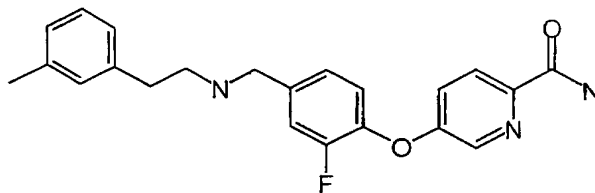
5-{2-Fluoro-4-[(2-pyridin-3-ylethylamino)methyl]phenoxy} pyridine-2-carboxamide



Using a method similar to Example 405, a reaction of 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.040 g, 0.154 mmol) and 2-(pyridin-3-yl)ethylamine (0.019 g, 0.154 mmol) gives the title compound (0.0463 g, 82.2%): TOF MS  $ES^+$  367.2 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{20}H_{20}N_4O_2F$  367.1570 ( $M+H$ ) $^+$ , found 367.1553, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min],  $t_R$  = 6.9 min, 100% purity.

**Example 408**

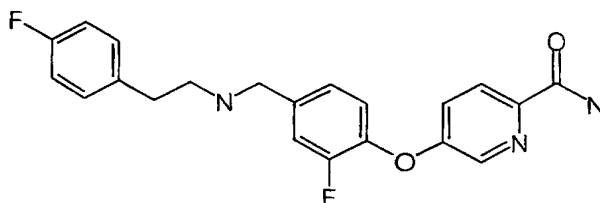
5-{2-Fluoro-4-[(2-*m*-tolylethylamino)methyl]phenoxy}pyridine-2-carboxamide



Using a method similar to Example 405, using 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 405, Part B) (0.040 g, 0.154 mmol) and 3-methylphenethylamine (0.021 g, 0.154 mmol) gives the title compound (0.0306 g, 52.5%): TOF MS  $ES^+$  380.2 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{21}H_{23}N_3O_2F$  380.1774 ( $M+H$ ) $^+$ , found 380.1757, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  = 8.4 min, 100% purity.

**Example 409**

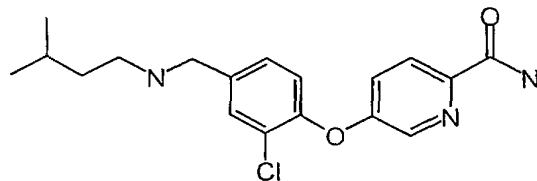
5-(2-Fluoro-4-{[2-(4-fluorophenyl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide



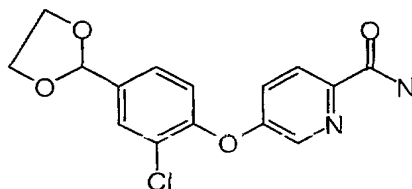
Using a method similar to Example 405, using 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.040 g, 0.154 mmol) and 4-fluorophenethylamine (0.021 g, 0.154 mmol) gives the title compound (0.0231 g, 39.2%): TOF MS  $ES^+$  384.2 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{21}H_{20}N_3O_2F_2$  384.1524 ( $M+H$ ) $^+$ , found 384.1509, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  = 7.8 min, 100% purity.

**Example 410**

5-{2-Chloro-4-[(3-methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide

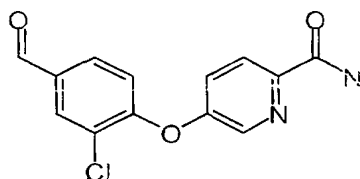


Part A: 5-(2-Chloro-4-[1,3]dioxolan-2-ylphenoxy)pyridine-2-carboxamide



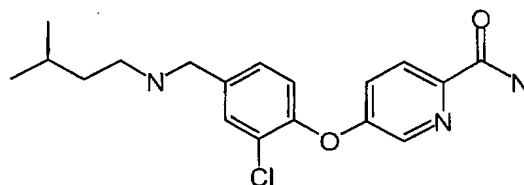
Using a method similar to Example 403, Part A, a reaction of 2-chloro-4-[1,3]dioxolan-2-ylphenol (Example 388, Part C2) (0.429 g, 2.14 mmol) and 5-fluoropyridine-2-carboxamide (Example 388 Part C) (0.299 g, 2.14 mmol) gives the title compound (0.264 g, 38.5%): MS ES<sup>+</sup> 320.9 (M+H)<sup>+</sup>; TLC [silica gel 60 F<sub>254</sub>, 30% ethyl acetate in dichloromethane] R<sub>f</sub> = 0.19

Part B: 5-(2-Chloro-4-formylphenoxy)pyridine-2-carboxamide



Using a method similar to Example 403, Part B, a reaction of 5-(2-chloro-4-[1,3]dioxolan-2-ylphenoxy)pyridine-2-carboxamide (0.263 g, 0.820 mmol) in 88% formic acid gives the title compound (0.194 g, 85.5%): TOF MS ES<sup>+</sup> 277.0 (M+H)<sup>+</sup>, HRMS calcd for C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>Cl 277.0380 (M+H)<sup>+</sup>, found 277.0378, time 0.38 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 10.3 min, 100% purity.

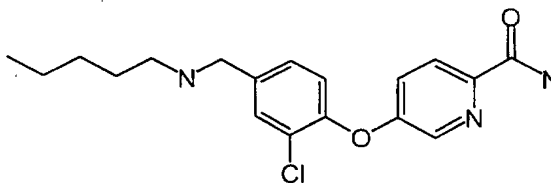
## Part C: 5-{2-Chloro-4-[(3-methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide



Using a method similar to Example 405, a reaction of 5-(2-chloro-4-formylphenoxy)pyridine-2-carboxamide (0.0388 g, 0.140 mmol) and isoamylamine (0.012 g, 0.140 mmol) gives the title compound (0.0320 g, 65.6%): TOF MS ES<sup>+</sup> 348.1 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>Cl 348.1479 (M+H)<sup>+</sup>, found 348.1466, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 7.4 min, 100% purity.

**Example 411**

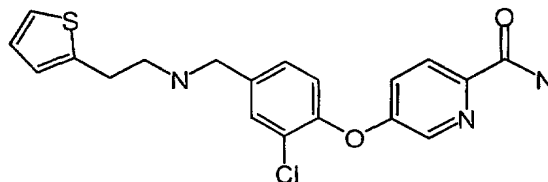
## 5-(2-Chloro-4-(pentylaminomethyl)phenoxy)pyridine-2-carboxamide



Using a method similar to Example 405, using 5-(2-chloro-4-formylphenoxy)pyridine-2-carboxamide (0.0388 g, 0.140 mmol) and amylamine (0.012 g, 0.140 mmol) gives the title compound (0.0314 g, 64.3%): TOF MS ES<sup>+</sup> 348.1 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>Cl 348.1479 (M+H)<sup>+</sup>, found 348.1456, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 7.6 min, 100% purity.

**Example 412**

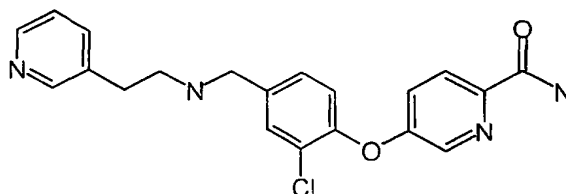
5-{2-Chloro-4-[(2-thiophen-2-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide



Using a method similar to Example 405, using 5-(2-chloro-4-formylphenoxy)pyridine-2-carboxamide (0.0388 g, 0.140 mmol) and 2-(2-thienyl)ethylamine (0.018 g, 0.140 mmol) gives the title compound (0.0396 g, 72.8%): TOF MS ES<sup>+</sup> 388.1 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>ClS 388.0887 (M+H)<sup>+</sup>, found 388.0866, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 7.6 min, 100% purity.

**Example 413**

5-{2-Chloro-4-[(2-pyridin-3-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide

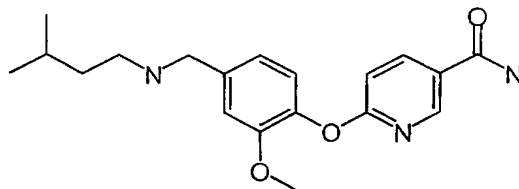


Using a method similar to Example 405, using 5-(2-chloro-4-formylphenoxy)pyridine-2-carboxamide (0.0388 g, 0.140 mmol) and 2-(pyridin-3-yl)ethylamine (0.017 g, 0.140 mmol) gives the title compound (0.0490 g, 91.2%): TOF MS ES<sup>+</sup> 383.1 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>Cl 383.1275 (M+H)<sup>+</sup>, found 383.1248, time 0.39 min; Anal. Calcd for C<sub>20</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>2</sub>•0.1CH<sub>2</sub>Cl<sub>2</sub>: C, 61.90; H, 5.06; N, 14.38. Found: C, 61.90; H, 5.06; N, 14.38.

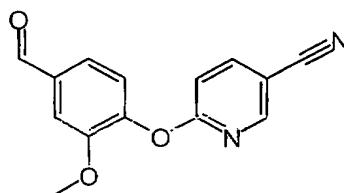


**Example 414**

6-{2-Methoxy-4-[(3-methylbutylamino)methyl]phenoxy}nicotinamide

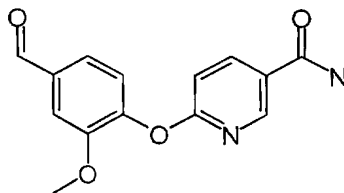


Part A: 6-(4-Formyl-2-methoxyphenoxy)nicotinonitrile



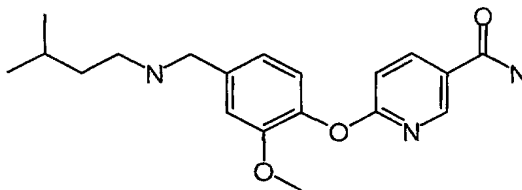
Take up vanillin (1.0 g, 6.57 mmol), 6-chloronicotinonitrile (0.911 g, 6.57 mmol) and  $K_2CO_3$  (1.36 g, 9.86 mmol) in DMF (16.4 mL). Stir at room temperature overnight, then heat at 100 °C for 3 hours. Cool the reaction mixture to room temperature before quenching with water (75 mL). Extract with dichloromethane (2 x 150 mL). Wash the organic layer with brine (1 x 75 mL), dry over  $MgSO_4$ , filter and concentrate to give the title compound (1.65 g, 98.8%): TOF MS  $ES^+$  255.1 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{14}H_{11}N_2O_3$  255.0770 ( $M+H$ ) $^+$ , found 255.0776, time 0.38 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  = 12.2 min, 100% purity.

Part B: 6-(4-Formyl-2-methoxyphenoxy)nicotinamide



Using a method similar to (Example 404, Part C), 6-(4-formyl-2-methoxyphenoxy)nicotinonitrile (1.53 g, 6.00 mmol) gives the title compound (1.59 g, 97.5%): MS  $ES^+$  273.0 ( $M+H$ ) $^+$ , MS  $ES^-$  271.1 ( $M-H$ ) $^-$ ; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  = 7.2 min, 98.6% purity.

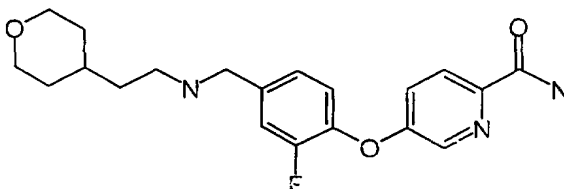
## Part C: 6-{2-Methoxy-4-[(3-methylbutylamino)methyl]phenoxy}nicotinamide



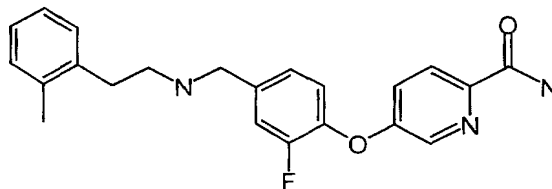
Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (0.0423 g, 0.155 mmol) and isoamylamine (0.020 g, 0.171 mmol) gives the title compound (0.0162 g, 30.3%): TOF MS ES<sup>+</sup> 344.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub> 344.1974 (M+H)<sup>+</sup>, found 344.1949, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 5.9 min, 100% purity.

**Example 415**

## 5-(2-Fluoro-4-{[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide



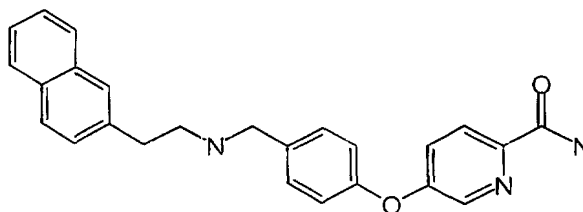
Using a method similar to Example 405, a reaction of 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.0294 g, 0.113 mmol) and 2-(tetrahydropyran-4-yl)ethylamine (0.016 g, 0.124 mmol) gives the title compound (0.0187 g, 44.2%): TOF MS ES<sup>+</sup> 374.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>F 374.1880 (M+H)<sup>+</sup>, found 374.1863, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 30-99% over 19 min], t<sub>R</sub> = 5.2 min, 95.2% purity.

**Example 416**5-{2-Fluoro-4-[(2-*o*-tolylethylamino)methyl]phenoxy}pyridine-2-carboxamide

Using a method similar to Example 405, using 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.0294 g, 0.113 mmol) and 2-methylphenethylamine (0.017 g, 0.124 mmol) gives the title compound (0.0276 g, 65.2%): TOF MS  $ES^+$  380.2 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{22}H_{23}N_3O_2F$  380.1774 ( $M+H$ ) $^+$ , found 380.1741, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 30-99% over 19 min],  $t_R$  = 8.2 min, 100% purity.

**Example 417**

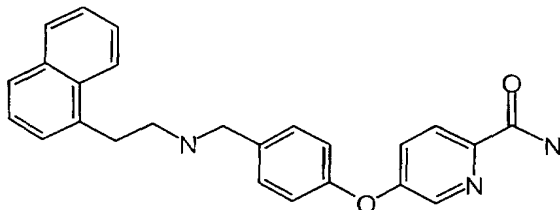
5-{4-[(2-Naphthalen-2-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide



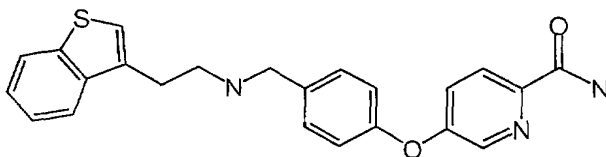
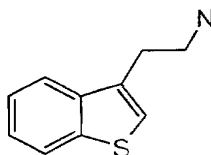
Using a method similar to Example 405, using 5-(4-formylphenoxy)pyridine-2-carboxamide (Example 388, Part D) (0.0366 g, 0.151 mmol) and 2-naphthalen-2-ylethylamine (0.0286 g, 0.166 mmol) gives the title compound (0.0302 g, 50.3%): TOF MS  $ES^+$  398.2 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{25}H_{24}N_3O_2$  398.1869 ( $M+H$ ) $^+$ , found 398.1833, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 30-99% over 19 min],  $t_R$  = 9.2 min, 98.0% purity.

**Example 418**

5-{4-[(2-Naphthalen-1-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide



Using a method similar to Example 405, a reaction of 5-(4-formylphenoxy)pyridine-2-carboxamide (Example 388, Part D) (0.0366 g, 0.151 mmol) and 2-naphthalen-1-ylethylamine (0.0285 g, 0.166 mmol) gives the title compound (0.0160 g, 26.7%): TOF MS ES<sup>+</sup> 398.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>25</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub> 398.1869 (M+H)<sup>+</sup>, found 398.1855, time 0.39min; TLC [silica gel 60 F<sub>254</sub>, 4% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate] R<sub>f</sub> = 0.26.

**Example 419**5-{4-[(2-Benzo[*b*]thiophen-3-ylethylamino)methyl]phenoxy}pyridine-2-carboxamidePart A: 2-Benzo[*b*]thiophen-3-ylethylamine

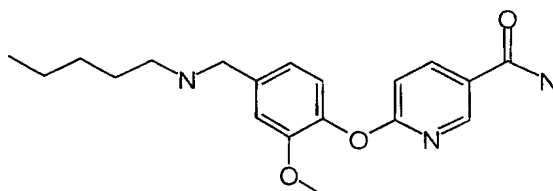
Reduce benzo[*b*]thiophen-3-yl-acetonitrile (350.9 mg, 2.0 mmol) in Et<sub>2</sub>O (6.0 mL) with 1.0 M LAH in THF (6.0 mL) at 0-10 °C for 1 hour. Carry out Fieser work-up to remove the LAH. Concentrate and pass through an SCX column, washing with MeOH and then eluting with 2.0 M NH<sub>3</sub> in MeOH. Concentrate the eluant and purify twice by chromatography, eluting with 75:20:5 EtOAc/hexanes/2.0 M NH<sub>3</sub> in MeOH and then with 70:20:10 EtOAc/hexanes/2.0 M NH<sub>3</sub> in MeOH to yield the title compound (86.5 mg, 24%): MS ES<sup>+</sup> 178.2 (M+H)<sup>+</sup>, 161.2 (base peak); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.94 (d, *J* = 7.3 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.40-7.33 (m, 3H), 3.32 (br s, 2H), 2.88 (br s, 4H).

Part B: 5-{4-[(2-Benzo[*b*]thiophen-3-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide

Using a method similar to Example 405, a reaction of 5-(4-formylphenoxy)pyridine-2-carboxamide (Example 388, Part D) (0.0366 g, 0.151 mmol) and 2-benzo[*b*]thiophen-3-ylethylamine (0.0295 g, 0.166 mmol) gives the title compound (0.0306 g, 50.2%): TOF MS ES<sup>+</sup> 404.1 (M+H)<sup>+</sup>, HRMS calcd for C<sub>23</sub>H<sub>22</sub>N<sub>3</sub>O<sub>2</sub>S 404.1433 (M+H)<sup>+</sup>, found 404.1423, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 8.9 min, 100% purity.

Example 420

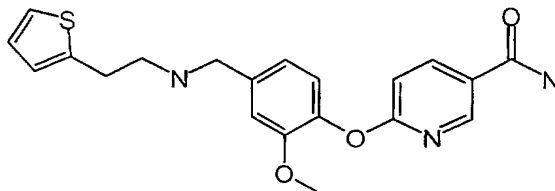
6-(2-Methoxy-4-pentylaminomethylphenoxy)nicotinamide



Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and amylamine (0.016 g, 0.184 mmol) gives the title compound (0.0426 g, 67.5%): TOF MS ES<sup>+</sup> 344.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub> 344.1974 (M+H)<sup>+</sup>, found 344.1963, time 0.41 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 6.1 min, 100% purity.

**Example 421**

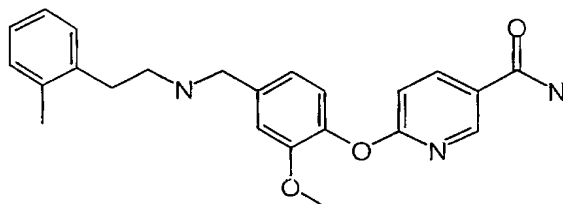
6-{2-Methoxy-4-[(2-thiophen-2-ylethylamino)methyl]phenoxy}nicotinamide



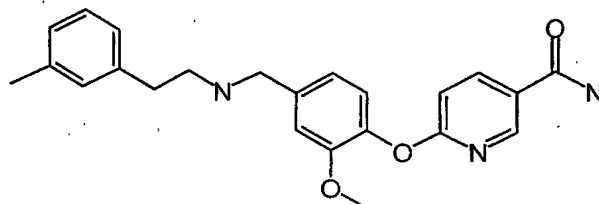
Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and 2-(2-thienyl)ethylamine (0.0234 g, 0.184 mmol) gives the title compound (0.0495 g, 70.3%): TOF MS ES<sup>+</sup> 384.1 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>22</sub>N<sub>3</sub>O<sub>3</sub>S 384.1382 (M+H)<sup>+</sup>, found 384.1375, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 6.1 min, 100% purity.

**Example 422**

6-{2-Methoxy-4-[(2-*o*-tolylethylamino)methyl]phenoxy}nicotinamide



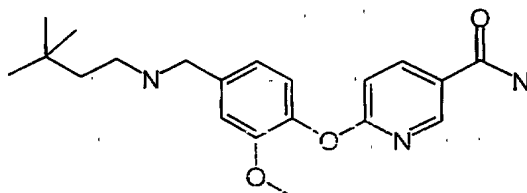
Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and 2-methylphenethylamine (0.0248 g, 0.184 mmol) gives the title compound (0.0584 g, 81.2%): TOF MS ES<sup>+</sup> 392.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>23</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub> 392.1974 (M+H)<sup>+</sup>, found 392.1966, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 7.5 min, 97.6% purity.

**Example 423**6-{2-Methoxy-4-[(2-*m*-tolylethylamino)methyl]phenoxy}nicotinamide

Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and 3-methylphenethylamine (0.0248 g, 0.184 mmol) gives the title compound (0.0568 g, 78.9%): TOF MS ES<sup>+</sup> 392.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>23</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub> 392.1974 (M+H)<sup>+</sup>, found 392.1975, time 0.41 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 7.7 min, 97.6% purity.

**Example 424**

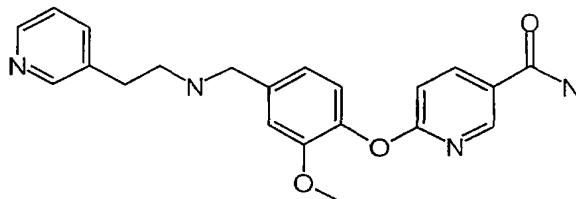
6-{4-[(3,3-Dimethylbutylamino)methyl]-2-methoxyphenoxy}nicotinamide



Using a method similar to Example 405, using 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and 3,3-dimethylbutylamine (0.0186 g, 0.184 mmol) gives the title compound (0.0205 g, 31.3%): TOF MS ES<sup>+</sup> 358.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>28</sub>N<sub>3</sub>O<sub>3</sub> 358.2131 (M+H)<sup>+</sup>, found 358.2131, time 0.41 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 6.8 min, 100% purity.

**Example 425**

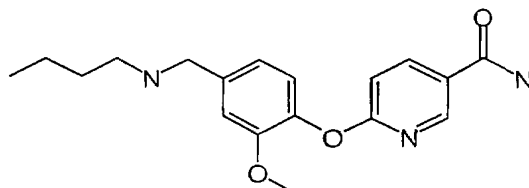
6-{2-Methoxy-4-[(2-pyridin-3-ylethylamino)methyl]phenoxy}nicotinamide



Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and 2-(pyridin-3-yl)ethylamine (0.0224 g, 0.184 mmol) gives the title compound (0.0406 g, 58.4%): TOF MS ES<sup>+</sup> 379.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>23</sub>N<sub>4</sub>O<sub>3</sub> 379.1770 (M+H)<sup>+</sup>, found 379.1759, time 0.41 min.

**Example 426**

6-(4-Butylaminomethyl-2-methoxyphenoxy)nicotinamide

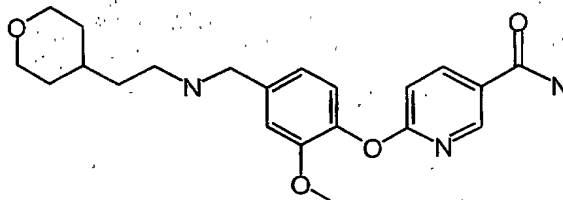


Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and *n*-butylamine (0.0134 g, 0.184 mmol) gives the title compound (0.0458 g, 75.7%): TOF MS ES<sup>+</sup> 330.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub> 330.1818 (M+H)<sup>+</sup>, found 330.1802, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 4.9 min, 100% purity.



**Example 427**

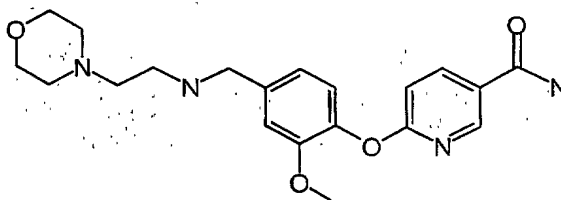
6-(2-Methoxy-4-{{2-(tetrahydropyran-4-yl)ethylamino}methyl}phenoxy)nicotinamide



Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and 2-(tetrahydropyran-4-yl)ethylamine (0.0237 g, 0.184 mmol) gives the title compound (0.0545 g, 77.0%): TOF MS ES<sup>+</sup> 386.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>4</sub> 386.2080 (M+H)<sup>+</sup>, found 386.2076, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 4.3 min, 100% purity.

**Example 428**

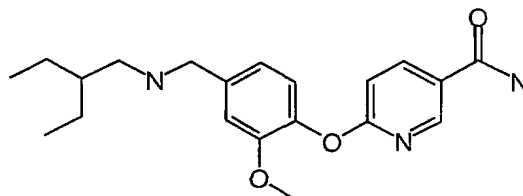
6-{2-Methoxy-4-[(2-morpholin-4-ylethylamino)methyl]phenoxy}nicotinamide



Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and 2-morpholin-4-ylethylamine (0.0224 g, 0.184 mmol) gives the title compound (0.0347 g, 49.0%): TOF MS ES<sup>+</sup> 387.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>27</sub>N<sub>4</sub>O<sub>4</sub> 387.2032 (M+H)<sup>+</sup>, found 387.2023, time 0.41 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.51 (d, *J* = 2.0 Hz, 1H), 8.19 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.98 (s, 2H), 7.43 (s, 1H), 7.11 (d, *J* = 1.95 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.91 (dd, *J* = 8.1, 1.7 Hz, 1H), 3.72 (s, 2H), 3.66 (s, 3H), 3.55 (t, *J* = 4.6 Hz, 4H), 2.63 (t, *J* = 6.6 Hz, 2H), 2.41 (t, *J* = 6.3 Hz, 2H), 2.34 (s, 4H).

**Example 429**

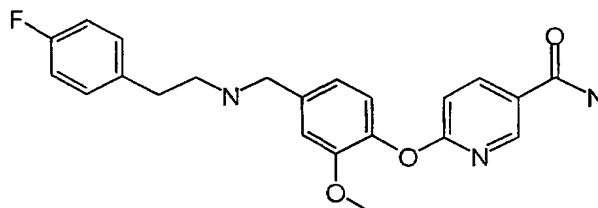
6-{4-[(2-Ethylbutylamino)methyl]-2-methoxyphenoxy}nicotinamide



Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and 2-ethylbutylamine (0.0186 g, 0.184 mmol) gives the title compound (0.0450 g, 68.6%): TOF MS  $ES^+$  358.2 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{20}H_{28}N_3O_3$  358.2131 ( $M+H$ ) $^+$ , found 358.2127, time 0.41 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  = 6.6 min, 98.8% purity.

**Example 430**

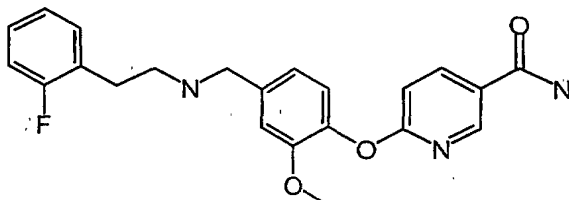
6-(4-{[2-(4-Fluorophenyl)ethylamino]methyl}-2-methoxyphenoxy)nicotinamide



Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and 4-fluorophenethylamine (0.0256 g, 0.184 mmol) gives the title compound (0.0689 g, 94.9%): TOF MS  $ES^+$  396.2 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{22}H_{23}N_3O_3F$  396.1723 ( $M+H$ ) $^+$ , found 396.1714, time 0.41 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  = 7.1 min, 100% purity.

**Example 431**

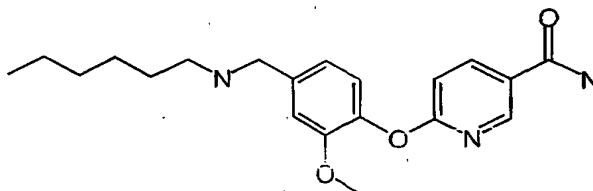
6-(4-{[2-(2-Fluorophenyl)ethylamino]methyl}-2-methoxyphenoxy)nicotinamide



Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and 2-fluorophenethylamine (0.0256 g, 0.184 mmol) gives the title compound (0.0615 g, 84.7%): TOF MS ES<sup>+</sup> 396.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>F 396.1723 (M+H)<sup>+</sup>, found 396.1722, min 0.39; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 6.8 min, 98.9% purity.

**Example 432**

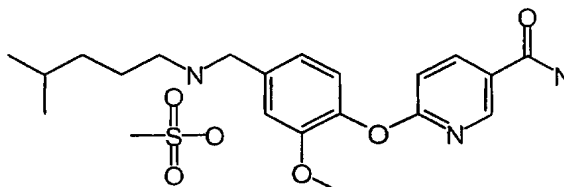
6-(4-Hexylaminomethyl-2-methoxyphenoxy)nicotinamide



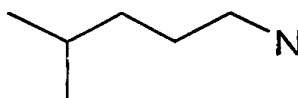
Using a method similar to Example 405, a reaction of 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.050 g, 0.184 mmol) and hexylamine (0.0186 g, 0.184 mmol) gives the title compound (0.0479 g, 73.0%): TOF MS ES<sup>+</sup> 358.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>28</sub>N<sub>3</sub>O<sub>3</sub> 358.2131 (M+H)<sup>+</sup>, found 358.2124, time 0.41 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min], t<sub>R</sub> = 7.4 min, 100% purity.

**Example 433**

6-{2-Methoxy-4-[(4-methylpentylamino)methyl]phenoxy}nicotinamide methanesulfonate



Part A: 4-Methylpentylamine



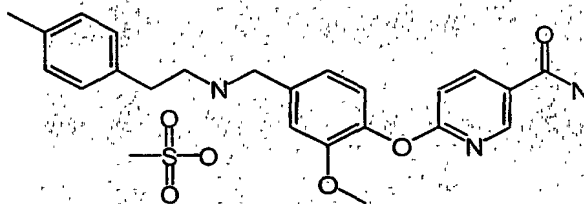
Stir a mixture of 4-methylpentanol (2.0 mL, 16.0 mmol), Et<sub>3</sub>N (4.5 mL, 32.1 mmol), and TsCl (3.676 g, 19.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at room temperature for 2 days. Quench the reaction with H<sub>2</sub>O, take up the mixture in Et<sub>2</sub>O (250 mL), and wash with 2.0 N HCl, H<sub>2</sub>O, 2.0 N NaOH, H<sub>2</sub>O and brine (100 mL each) consecutively. Back-extract the aqueous washings with Et<sub>2</sub>O (200 mL). Combine the organic layers, dry over MgSO<sub>4</sub> and concentrate.

Dissolve the tosylate obtained in 7.0 N NH<sub>3</sub> in MeOH (200 mL) at 0 °C. Stir for 5 days, while allowed to warm to room temperature. Concentrate and purify on an SCX column, washing with MeOH, then eluting with 2.0 M NH<sub>3</sub> in MeOH. Repeat the process three times till no amine was observed in MeOH washings. Combine the eluants and carefully distill to collect the title amine (610.7 mg, 37%): bp 90-110 °C; GCMS 101 (M)<sup>+</sup>, 4.46 min.

Part B: 6-{2-Methoxy-4-[(4-methylpentylamino)methyl]phenoxy}nicotinamide methanesulfonate Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.100 g, 0.367 mmol), 4-methylpentylamine (Part A, 0.0409 g, 0.404 mmol) and 3Å molecular sieves in a vial. Add methanol (3.6 mL), cap and stir overnight. Add NaBH<sub>4</sub> (in excess over two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 5 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 10 g ISCO® column with (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give 6-{2-methoxy-4-[(4-methylpentylamino)methyl]phenoxy}nicotinamide (0.131 g, 71.8%). Dissolve the compound in dichloromethane (2.5 mL) and add 1 equivalent of 0.50 M methanesulfonic acid in dichloromethane. Stir the solution for a short time before concentrating to give the title compound (0.124 g, ~100%): TOF MS ES<sup>+</sup> 358.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>28</sub>N<sub>3</sub>O<sub>3</sub> 358.2131 (M+H)<sup>+</sup>, found 358.2119, time 0.39 min; HPLC [Waters XTerra™ MS C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 15 min], t<sub>R</sub> = 8.2 min, 100% purity.

#### Example 434

6-{2-Methoxy-4-[(2-*p*-tolylethylamino)methyl]phenoxy}nicotinamide methanesulfonate

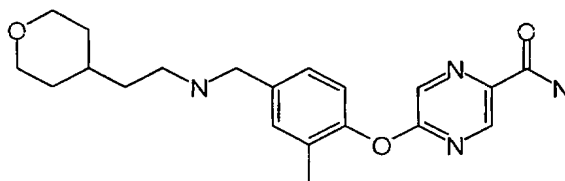


Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.100 g, 0.367 mmol), 2-*p*-tolylethylamine (0.0546 g, 0.404 mmol) and 3Å molecular sieves in a vial. Add methanol (3.6 mL), cap and stir overnight. Add NaBH<sub>4</sub> (in excess over two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 5 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 10 g ISCO® column with (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give 6-{2-methoxy-4-[(2-*p*-tolylethylamino)methyl]phenoxy}nicotinamide (0.143 g, 97.8%). Dissolve the compound in dichloromethane (2.5 mL) and add 1 equivalent of 0.50 M methanesulfonic acid in dichloromethane. Stir the solution for a

short time before concentrating to give the title compound (0.168 g, ~100%): TOF MS  $ES^+$  392.1 (M+H) $^+$ , HRMS calcd for  $C_{23}H_{26}N_3O_3$  392.1974 (M+H) $^+$ , found 392.1966, time 0.39 min; HPLC [Waters XTerra<sup>TM</sup> MS C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 15 min],  $t_R$  = 8.4 min, 100% purity.

### Example 435

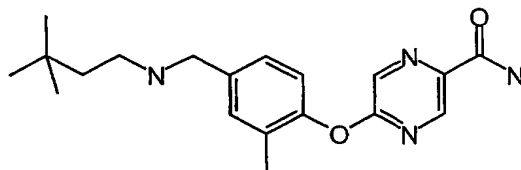
5-(2-Methyl-4- {[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)pyrazine-2-carboxamide



Place 5-(4-formyl-2-methylphenoxy)pyrazine-2-carboxamide (Example 404, Part D) (0.200 g, 0.777 mmol), 2-(tetrahydropyran-4-yl)ethylamine (0.100 g, 0.777 mmol) and 3Å molecular sieves in a vial. Add methanol (3.8 mL), cap and stir overnight. Add  $NaBH_4$  (in excess over two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 5 g ISCO<sup>®</sup> pre-load column. Dry the pre-loaded column in a vacuum oven at room temperature. Purify by eluting through a 10 g ISCO<sup>®</sup> column with (2.0 M  $NH_3$  in methanol), ethyl acetate and hexanes. After concentrating, take the product up in  $CH_2Cl_2$  (25 mL) and wash with 1.0 N NaOH solution (2 x 10 mL). Dry the organic layer over  $Na_2SO_4$ , filter and concentrate to give the title compound (0.121 g, 42.0%): MS  $ES^+$  371.1 (M+H) $^+$ , base peak 242.0 (M- $C_7H_{14}NO$ ) $^+$ ; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min],  $t_R$  = 7.9 min, 100% purity.

**Example 436**

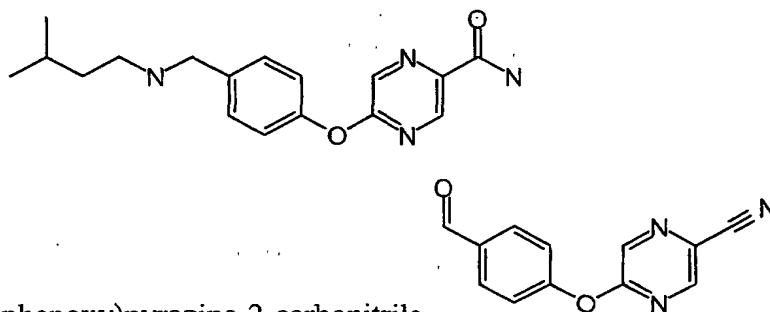
5-{4-[(3,3-Dimethylbutylamino)methyl]-2-methylphenoxy}pyrazine-2-carboxamide



Place 5-(4-formyl-2-methylphenoxy)pyrazine-2-carboxamide (Example 404, Part D) (0.200 g, 0.777 mmol), 3,3-dimethylbutylamine (0.100 g, 0.777 mmol) and 3 Å molecular sieves in a vial. Add methanol (3.8 mL), cap and stir overnight. Add NaBH<sub>4</sub> (in excess over two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 5 g ISCO® pre-load column. Dry the pre-loaded column in a vacuum oven at room temperature. Purify by eluting through a 10 g ISCO® column with (2.0 M NH<sub>3</sub> in methanol), ethyl acetate and hexanes. After concentrating, take the product up in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and wash with 1.0 N NaOH solution (2 x 10 mL). Dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate to give the title compound (0.110 g, 41.4%): MS ES<sup>+</sup> 343.1 (M+H)<sup>+</sup>, base peak 242.0 (M-C<sub>6</sub>H<sub>14</sub>N)<sup>+</sup>; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 9.7 min, 94.3% purity.

**Example 437**

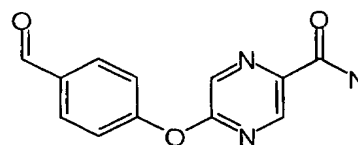
5-{4-[(3-Methylbutylamino)methyl]phenoxy}pyrazine-2-carboxamide



Part A: 5-(4-Formylphenoxy)pyrazine-2-carbonitrile

Dissolve 4-[1,3]dioxolan-2-yl-2-phenol (Example 388, Part C2) (1.70 g, 10.2 mmol), 5-chloropyrazine-2-carbonitrile (Example 404, Part A) (1.50 g, 10.7 mmol) and K<sub>2</sub>CO<sub>3</sub> (3.71 g, 26.9 mmol) in DMA (27.0 mL) and isooctane (13.4 mL). Heat at 110 °C for about 2.25 hours. Cool to room temperature and quench with water (100 mL).

Extract with dichloromethane (3 x 100 mL). Wash the extract with saturated aqueous  $\text{NaHCO}_3$  (1 x 50 mL) and brine (1 x 75 mL). Dry the organic layer over  $\text{Na}_2\text{SO}_4$ , filter and concentrate. Purify by flash chromatography, eluting with 0–30% ethyl acetate in hexanes. Concentrate the eluant, then take the solid up in 88% formic acid (46 mL) and stir at room temperature for 4 hours. Dilute the reaction mixture with water (50 mL). Extract with dichloromethane (2 x 100 mL). Wash the extract with saturated aqueous  $\text{NaHCO}_3$  (1 x 50 mL), dry over  $\text{Na}_2\text{SO}_4$ , filter and concentrate. Purify by flash chromatography eluting with 30% ethyl acetate in hexanes to give the title compound (1.88 g, 77.7%): TOF MS  $\text{ES}^+$  225.1 (M) $^+$ , HRMS calcd for  $\text{C}_{12}\text{H}_7\text{N}_3\text{O}_2$  225.0538 (M) $^+$ , found 225.0527, time 0.38 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20–99% over 23 min],  $t_R$  = 11.5 min, 100% purity.



Part B: 5-(4-Formylphenoxy)pyrazine-2-carboxamide

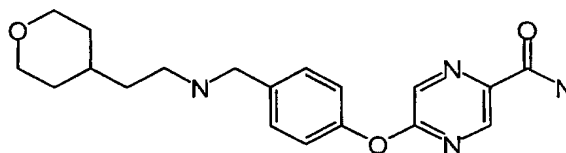
Dissolve 5-(4-formylphenoxy)pyrazine-2-carbonitrile (1.87 g, 8.30 mmol) and  $\text{K}_2\text{CO}_3$  (0.573 g, 4.15 mmol) in DMSO (21 mL). Add 30%  $\text{H}_2\text{O}_2$  (2.4 mL, 20.8 mmol) and stir at room temperature for 22 hours. Add additional  $\text{K}_2\text{CO}_3$  (0.573 g, 4.15 mmol) and heat at 55 °C for about 2.5 hours. Cool the reaction mixture and dilute with  $\text{CH}_2\text{Cl}_2$  (200 mL). Wash with water (1 x 100 mL) and saturated aqueous  $\text{NaHCO}_3$  (1 x 100 mL). Dry the organic layer over  $\text{Na}_2\text{SO}_4$ , filter and concentrate. Purify by flash chromatography, eluting with 0–50% ethyl acetate in dichloromethane to give the title compound (0.478 g, 23.7%): TOF MS  $\text{ES}^+$  244.1 (M+H) $^+$ , HRMS calcd for  $\text{C}_{12}\text{H}_{10}\text{N}_3\text{O}_3$  244.0722 (M+H) $^+$ , found 244.0709, time 0.38 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20–99% over 23 min],  $t_R$  = 7.2 min, 100% purity.



Part C: 5-{4-[(3-Methylbutylamino)methyl]phenoxy}pyrazine-2-carboxamide Place 5-(4-formylphenoxy)pyrazine-2-carboxamide (0.150 g, 0.617 mmol), 3-methylbutylamine (0.0537 g, 0.617 mmol) and 3Å molecular sieves in a vial. Add methanol (3.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (in excess over two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 5 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 10 g ISCO® column with 2.0 M NH<sub>3</sub> in methanol, ethyl acetate and hexanes to give the title compound (0.0606 g, 31.2%): MS ES<sup>+</sup> 315.1 (M+H)<sup>+</sup>, base peak 228.0 (M-C<sub>5</sub>H<sub>12</sub>N)<sup>+</sup>; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 8.5 min, 96.4% purity.

#### Example 438

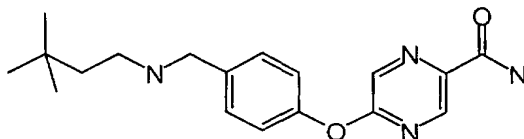
5-(4-{[2-(Tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)pyrazine-2-carboxamide



Place 5-(4-formylphenoxy)pyrazine-2-carboxamide (Example 437, Part B) (0.150 g, 0.617 mmol), 2-(tetrahydropyran-4-yl)ethylamine (0.0797 g, 0.617 mmol) and 3Å molecular sieves in a vial. Add methanol (3.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (in excess over two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 5 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 10 g ISCO® column with 2.0 M NH<sub>3</sub> in methanol and ethyl acetate. After concentrating, take the product up in dichloromethane (25 mL) and wash with 1.0 N NaOH solution (2 x 10 mL). Dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate to give the title compound (0.0819 g, 37.2%): MS ES<sup>+</sup> 357.1 (M+H)<sup>+</sup>, base peak 228.0 (M-C<sub>7</sub>H<sub>14</sub>NO)<sup>+</sup>; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 7.4 min, 100% purity.

**Example 439**

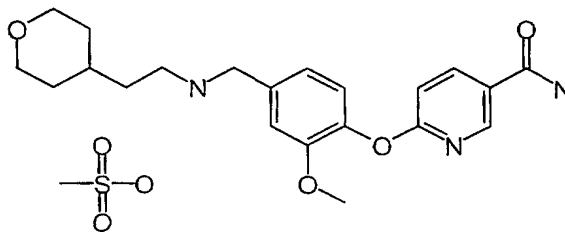
5-{4-[(3,3-Dimethylbutylamino)methyl]phenoxy}pyrazine-2-carboxamide



Place 5-(4-formylphenoxy)pyrazine-2-carboxamide (Example 437, Part B) (0.150 g, 0.617 mmol), 3,3-dimethylbutylamine (0.0624 g, 0.617 mmol) and 3 Å molecular sieves in a vial. Add methanol (3.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (in excess over two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 5 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 10 g ISCO® column with 2.0 M NH<sub>3</sub> in methanol, ethyl acetate and hexanes. After concentrating, take the product up in dichloromethane (25 mL) and wash with 1.0 N NaOH solution (2 x 10 mL). Dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate to give the title compound (0.0687 g, 33.8%): MS ES<sup>+</sup> 329.1 (M+H)<sup>+</sup>, base peak 228.0 (M-C<sub>6</sub>H<sub>15</sub>N)<sup>+</sup>; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 9.2 min, 100% purity.

**Example 440**

6-(2-Methoxy-4-{[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)nicotinamide methanesulfonate

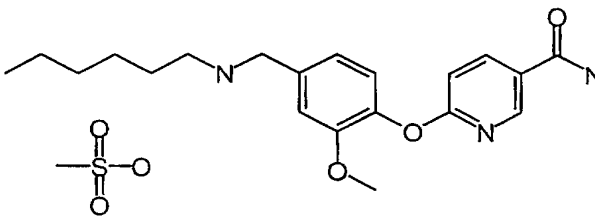


Dissolve 6-(2-methoxy-4-{[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)nicotinamide (Example 427) (0.612, 1.59 mmol) in THF (4 mL) and few drops of methanol to form a clear solution. Add 1.27 M methanesulfonic acid (1.25 mL, 1.59 mmol) in THF. Stir for 10 minutes, then concentrate to give the title compound (0.749 g, ~100%): TOF MS ES<sup>+</sup> 386.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>4</sub>

386.2080 (M+H)<sup>+</sup>, found 386.2083, time 0.62 min; HPLC [Waters XTerra<sup>TM</sup> MS C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 15 min], t<sub>R</sub> = 6.6 min, 100% purity.

#### Example 441

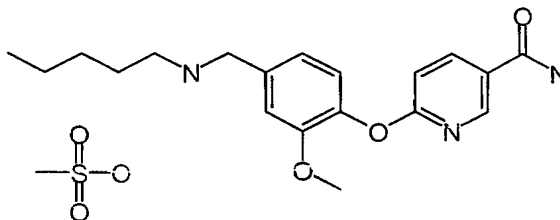
6-(4-Hexylaminomethyl-2-methoxyphenoxy)nicotinamide methanesulfonate



Using a procedure similar to that of Example 440, using 6-(4-hexylaminomethyl-2-methoxyphenoxy)nicotinamide (Example 432) the title compound is obtained.

#### Example 442

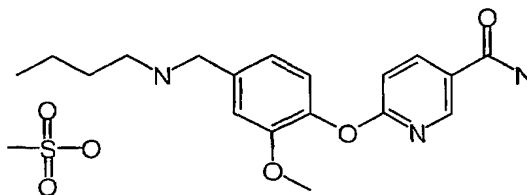
6-(2-Methoxy-4-pentylaminomethylphenoxy)nicotinamide methanesulfonate



Using a procedure similar to that of Example 440, using 6-(2-methoxy-4-pentylaminomethylphenoxy)nicotinamide (Example 420) the title compound is obtained.

**Example 443**

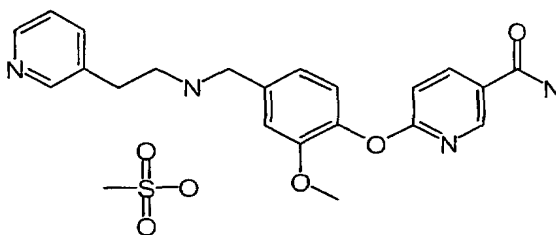
6-(4-Butylaminomethyl-2-methoxyphenoxy)nicotinamide methanesulfonate



Using a procedure similar to that of Example 440, using 6-(4-butylaminomethyl-2-methoxyphenoxy)nicotinamide (Example 426) the title compound is obtained.

**Example 444**

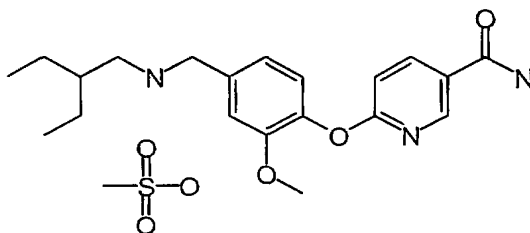
6-{2-Methoxy-4-[(2-pyridin-3-ylethylamino)methyl]phenoxy} nicotinamide  
methanesulfonate



Using a procedure similar to that of Example 440, using 6-{2-methoxy-4-[(2-pyridin-3-ylethylamino)methyl]phenoxy}nicotinamide (Example 425) the title compound is obtained.

**Example 445**

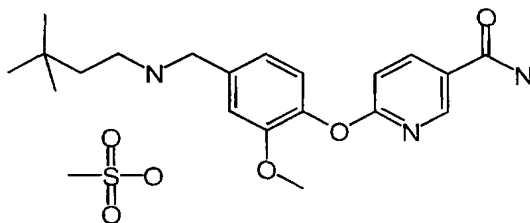
6-{4-[(2-Ethylbutylamino)methyl]-2-methoxyphenoxy}nicotinamide methanesulfonate



Using a procedure similar to that of Example 440, using 6-{4-[(2-ethylbutylamino)methyl]-2-methoxyphenoxy}nicotinamide (Example 429) the title compound is obtained.

**Example 446**

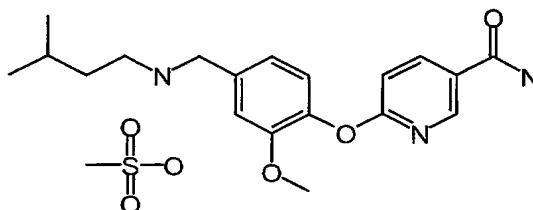
6-{4-[(3,3-Dimethylbutylamino)methyl]-2-methoxyphenoxy}nicotinamide  
methanesulfonate



Using a procedure similar to that of Example 440, using 6-{4-[(3,3-dimethylbutylamino)methyl]-2-methoxyphenoxy}nicotinamide (Example 424) the title compound is obtained.

**Example 446A**

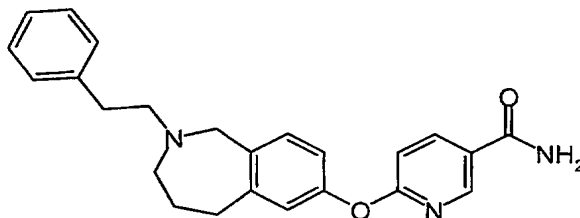
6-{2-Methoxy-4-[(3-methylbutylamino)methyl]phenoxy}nicotinamide methanesulfonate



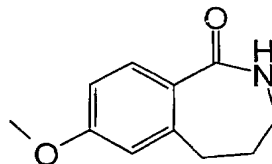
Using a procedure similar to that of Example 440, using 6-{2-methoxy-4-[(3-methylbutylamino)methyl]phenoxy}nicotinamide (Example 414, Part C) the title compound is obtained.

**Example 447**

6-(2-Phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide



Part A: 7-Methoxy-2,3,4,5-tetrahydro-benzo[*c*]azepin-1-one

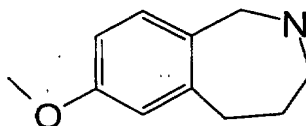


Dissolve 4-hydroxytetralone (50 g, 284 mmol) in methanesulfonic acid (400 mL) and chill to 2 °C in an ice bath. Add sodium azide (24 g, 369 mmol) in 3-gram portions over a period of 3 hours while keeping the temperature below 5 °C. Stir the solution cold for an additional hour and allow gradually warm to room temperature by removing the ice bath. Stir the solution for 16 hours. Pour the mixture into 3 L of crushed ice and add saturated aqueous NaHCO<sub>3</sub> until a pH of 8 is achieved. Add EtOAc (4 L) and extract 3 times. Dry the organic layer over MgSO<sub>4</sub> and concentrate to a white solid.

Chromatography on a Biotage® 75 S column (eluant 10:1 hexanes/EtOAc) provides the title compound as a white solid (27.3 g, 50 % of theory). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.90 (br

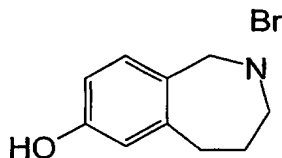
t, 1 H), 7.48 (d, 1 H), 6.89 (m, 2 H), 3.72 (s, 3 H), 2.90 (m, 2 H), 2.59 (t, 2 H) 1.83 (m, 2 H).

Part B: 7-Methoxy-2,3,4,5,5-tetrahydro-benzo[c]azepine



Add 7-methoxy-2,3,4,5-tetrahydro-benzo[c]azepin-1-one from step A (10 g, 53 mmol) to THF (50 mL) under a nitrogen atmosphere. Stir and chill the solution to 0 °C in an ice bath and add drop wise borane-THF complex (156 ml, 1.0 M in THF, 156 mmol). After complete addition, heat the solution at reflux for 2 hours and then cool to room temperature. Quench the reaction with 1.0 N HCl solution. Adjust the pH to 9 with 1.0 N NaOH solution and add 300 mL of EtOAc. Extract the solution, dry the organic layer over MgSO<sub>4</sub> and concentrate to a yellow oil. Chromatography on a Biotage® 75 S column (10% MeOH/DCM) yields the title compound as a white solid (4.2 g; 45 % of theory). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.00 (d, 1 H), 6.63 (s, 1H), 6.59 (dd, 1 H), 3.69 (s, 2H), 3.67 (s, 3 H), 3.02 (t, 2 H), 2.72 (m, 2 H), 1.55 (m, 2 H). MS (EI) 178.2 m/z (M+1)

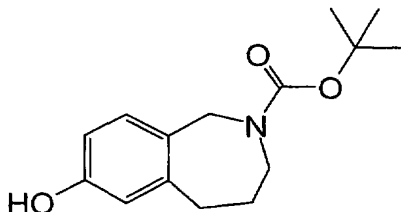
Part C: 2,3,4,5-Tetrahydro-1*H*-benzo[c]azepin-7-ol Hydrobromide



Dissolve product from Step B above (4.2 g, 22 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and add to BBr<sub>3</sub> (67 mmol, 6.4 mL) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at -78 °C under a nitrogen atmosphere. Stir the reaction mixture at -70 °C for 2 hours and then at room temperature for 16 hours. Cool the clear solution to -78 °C and carefully add methanol (15 mL). Concentrate the solution to a brown solid. Dissolved the solid in methanol (50 mL) and add CH<sub>2</sub>Cl<sub>2</sub> (40 mL). Concentrate the solution to half-volume and add hexanes (40 mL). Concentrate again to half volume and add EtOAc (20 mL). Concentrate to a volume to 20 mL and filter to obtain a white granular solid (4.2 g, 45 % of theory): <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.52 (s, 1H), 8.70 (br, 2H), 7.19 (d, 1H), 6.58 (m, 2H), 4.23 (s, 2H), 3.33 (m, 2H), 2.88 (m,

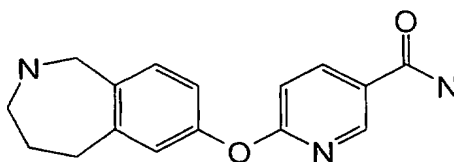
2H), 1.70 (m, 2H). MS (ES) 164.1 m/z (M+1). Elemental analysis Calc C 49.19, H 5.78, N 5.55; Found C 49.48, H 5.78, N 5.55.

Part D: *N*-*tert*-Butoxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-ol



Mix product from Step C above (6.50 g, 26 mmol) with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) to form a slurry. Add triethylamine (79 mmol) and cool the slurry to 5 °C in an ice bath. Dissolve di-*tert*-butyl dicarbonate in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and add drop wise to the solution. Remove the ice bath and allow the solution to stir at room temperature for four hours. Concentrate the solution to a brown solid. Add 40 ml of a 1:1 CH<sub>2</sub>Cl<sub>2</sub>/EtOAc solution and filter. Concentrate the filtrate to a brown oil and chromatograph (20% EtOAc/hexanes) to give a white solid (6.3 g, 90 % of theory): <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.15 (s, 1H), 6.97 (d, 1H), 6.60 (s, 1H), 6.49 (d, 1H), 4.23 (s, 2H), 3.52 (br m, 2H), 2.72 (br m, 2H), 1.59 (br m, 2H), 1.33 (s, 9H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 156.24, 142.99, 129.41, 116.41, 111.57, 78.29, 50.95, 49.57, 34.58, 28.02. Anal. Calcd for C<sub>15</sub>H<sub>21</sub>NO<sub>3</sub>: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.54; H, 8.15; N, 5.24.

Part E: 6-(2,3,4,5-Tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide



Add 80% NaH in mineral oil (28.3 mg, 0.94 mmol) to a solution of the benzazepinol in Part D (124.3 mg, 0.47 mmol) in anhydrous DMF (2.0 mL) and stir for 30 minutes at room temperature. Add 6-chloronicotinamide (147.8 mg, 0.94 mmol) in one portion and stir overnight at room temperature and then heat at 80 °C for 3 hours. Quench the reaction with water and concentrate. Purify by flash chromatography, eluting with 40% CH<sub>2</sub>Cl<sub>2</sub> in EtOAc.



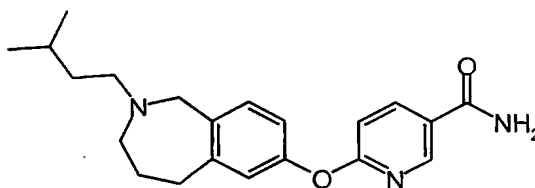
Dissolve the above-coupled product in  $\text{CH}_2\text{Cl}_2$  (2.5 mL) and treat with trifluoroacetic acid (2.5 mL) at room temperature for one hour. Concentrate the mixture and purify by an SCX column, washing with methanol and then eluting with 2.0 M  $\text{NH}_3$  in MeOH to yield the title compound (109.3 mg, 82% for 2 steps): MS  $\text{ES}^+$  284.0 ( $\text{M}-\text{H}^+$ ); HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min],  $t_R$  = 6.99 min, 100% purity.

**Part F: 6-(2-Phenethyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-7-yloxy)nicotinamide**

Mix 6-(2,3,4,5-tetrahydro-1H-benzo[c]azepin-7-yloxy)nicotinamide (Part E, 112.9 mg, 0.40 mmol),  $\text{K}_2\text{CO}_3$  (110.1 mg, 0.80 mmol), and phenethyl bromide (82  $\mu\text{L}$ , 0.60 mmol) in DMF (2.0 mL). Heat at 70-80 °C overnight. Remove DMF azeotropically with xylenes. Purify by flash chromatography, eluting with 75:19:6 EtOAc/ $\text{CH}_2\text{Cl}_2$ /2.0 M  $\text{NH}_3$  in MeOH and then with 60:30:10 EtOAc/hexanes/2.0 M  $\text{NH}_3$  in MeOH. Purify by reverse phase chromatography, eluting with 0-99% 0.1% TFA/acetonitrile and 0.1% TFA/water to give the title compound (44.9 mg, 27% from Step D): MS  $\text{ES}^+$  284.0 ( $\text{M}-\text{H}^+$ ); HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min],  $t_R$  = 9.85 min, 100% purity; Anal. Calcd for  $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_2 \cdot 0.1\text{H}_2\text{O} \cdot 0.1\text{MeOH}$ : C, 73.75; H, 6.57; N, 10.71. Found: C, 73.45; H, 6.62; N, 10.72.

**Example 448**

**6-[2-(3-Methylbutyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-7-yloxy]nicotinamide**

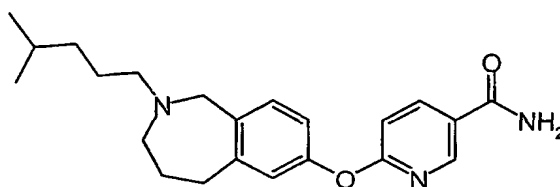


Mix 6-(2,3,4,5-tetrahydro-1H-benzo[c]azepin-7-yloxy)nicotinamide (Example 447, Part E, 50.7 mg, 0.18 mmol),  $\text{K}_2\text{CO}_3$  (49.5 mg, 0.36 mmol), and isoamyl bromide (32  $\mu\text{L}$ , 0.27 mmol) in DMF (1.0 mL). Heat at 80 °C for 6 hours. Pass through an SCX column, washing with methanol and then eluting with 2.0 M  $\text{NH}_3$  in MeOH. Concentrate the eluant and purify by flash chromatography, eluting with 70:22:8 EtOAc/ $\text{CH}_2\text{Cl}_2$ /2.0 M  $\text{NH}_3$  in MeOH to afford the title compound (45.7 mg, 72%): MS  $\text{ES}^+$  354.0 ( $\text{M}+\text{H}^+$ ),

HRMS calcd for  $C_{21}H_{28}N_3O_2$  354.2182 ( $M+H$ )<sup>+</sup>, found 354.2182, time 0.39 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 20-99% over 23 min],  $t_R$  = 6.39 min, 100% purity; Anal. Calcd for  $C_{21}H_{27}N_3O_2 \cdot 0.2CH_2Cl_2 \cdot 0.1MeOH$ : C, 69.59; H, 5.98; N, 11.43. Found: C, 69.47; H, 6.25; N, 11.30.

#### Example 449

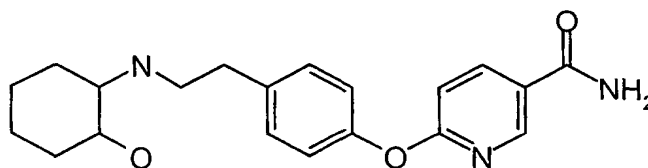
6-[2-(3-Methylpentyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy]nicotinamide



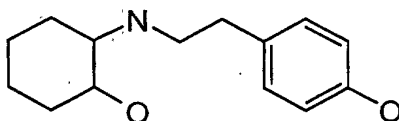
Mix 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide (Example 447, Part E, 55.6 mg, 0.20 mmol),  $K_2CO_3$  (54.2 mg, 0.39 mmol), and 1-bromo-4-methylpentane (43  $\mu$ L, 0.29 mmol) in DMF (1.0 mL). Heat at 80 °C overnight. Remove DMF azeotropically with xylenes. Purify by flash chromatography, eluting with 70:25:5 EtOAc/ $CH_2Cl_2$ /2.0 M  $NH_3$  in MeOH to afford the title compound (43.1 mg, 60%): MS  $ES^+$  368.4 ( $M+H$ )<sup>+</sup>, HRMS calcd for  $C_{22}H_{30}N_3O_2$  368.2338 ( $M+H$ )<sup>+</sup>, found 368.2330, time 0.39 min; Anal. Calcd for  $C_{22}H_{29}N_3O_2 \cdot 0.1CH_2Cl_2 \cdot 0.1MeOH$ : C, 70.32; H, 7.87; N, 11.08. Found: C, 70.05; H, 7.52; N, 11.01.

#### Example 450

( $\pm$ )-6-{4-[2-(2-Hydroxycyclohexylamino)ethyl]phenoxy}nicotinamide



## Part A: (±)-4-[2-(2-Hydroxycyclohexylamino)ethyl]phenol



Mix (±)-2-aminocyclohexanol (1.5227 g, 13.2 mmol),  $K_2CO_3$  (4.56 g, 33.0 mmol), and 1-(2-chloroethyl)-4-methoxybenzene (2.0 mL, 13.2 mmol) in DMF (30 mL). Heat at 100 °C for 24 hours. Cool down to room temperature and filtrate with MeOH wash. Concentrate and remove DMF azeotropically with xylenes. Take up the residue in  $CH_2Cl_2$  and  $H_2O$  (100 mL each). Separate the layers and extract the aqueous layer with  $CH_2Cl_2$  (2 x 100 mL). Wash the organic layers with  $H_2O$  and brine (100 mL each). Dry the combined organic layers over  $MgSO_4$ , concentrate and purify by flash chromatography, eluting with 50:45:5 EtOAc/ $CH_2Cl_2$ /2.0 M  $NH_3$  in MeOH to afford 2-(4-methoxyphenethylamino)cyclohexanol. (1.38 g, 42%).

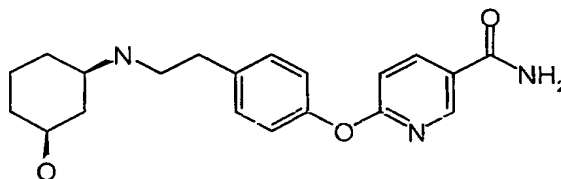
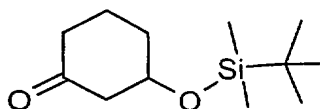
Mix the methoxy ether (505.9 mg, 2.0 mmol) and 1.0 M  $BBr_3$  in heptane (4.0 mL, 4.0 mmol) in  $CH_2Cl_2$  (10 mL in total). Stir the mixture at 0-17 °C for 3 hours. Quench the reaction with saturated aqueous  $NaHCO_3$  (30 mL) at 0 °C. Take up the mixture in saturated aqueous  $NaHCO_3$  (20 mL) and  $CH_2Cl_2$  (30 mL). Dissolve the precipitate formed with  $CH_2Cl_2$  and a small amount of MeOH. Separate the layers after vigorously shaking. Wash the organic layer with 1:1 saturated aqueous  $NaHCO_3$ /brine (50 mL). Back-extract the aqueous layers with  $CH_2Cl_2$  (2 x 50 mL) and 10% MeOH in  $CH_2Cl_2$  (5 x). Dry the combined organic layers over  $MgSO_4$ , concentrate and purify by flash chromatography, eluting with 75:15:10 EtOAc/ $CH_2Cl_2$ /2.0 M  $NH_3$  in MeOH (375.8 mg, 79%); MS  $ES^+$  236.1 (M+H) $^+$ ,  $ES^-$  234.2 (M-H) $^-$ ;  $^1H$  NMR ( $DMSO-d_6$ )  $\delta$  9.11 (s, 1H), 6.97 (d,  $J$  = 8.3 Hz, 2H), 6.93 (d,  $J$  = 8.3 Hz, 2H), 4.41 (d,  $J$  = 4.4 Hz, 1H), 3.32 (s, 1H), 3.03 (s, 1H), 2.76 (m, 1H), 2.55 (m, 3H), 2.14 (m, 1H), 1.87 (m, 1H), 1.75 (m, 1H), 1.54 (m, 2H), 1.13 (m, 3H), 0.86 (m, 1H).

## Part B: (±)-6-{4-[2-(2-Hydroxycyclohexylamino)ethyl]phenoxy}nicotinamide

Heat a mixture of 4-[2-(2-hydroxycyclohexylamino)ethyl]phenol (152.6 mg, 0.65 mmol), 6-chloronicotinamide (84.6 mg, 0.54 mmol) and  $K_2CO_3$  (186.7 mg, 1.35 mmol) in 3:1 DMF/toluene (4.0 mL) at 160 °C for 2 hours. Cool to room temperature and filter with thorough MeOH and  $CH_2Cl_2$  wash. Concentrate the filtrate and remove DMF azeotropically with xylenes. Purify by flash chromatography, eluting with 75:15:10 EtOAc/ $CH_2Cl_2$ /2.0 M  $NH_3$  in MeOH (56.3 mg, 29%): MS  $ES^+$  356.1 (M+H) $^+$ , HRMS calcd for  $C_{20}H_{26}N_3O_3$  356.1974(M+H) $^+$ , found 356.1966, time 0.37 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), acetonitrile in water containing 0.01% concentrated HCl at 1.0 mL/min, 30-99% over 19 min],  $t_R$  = 1.23 min, 100% purity; Chiralpak AD 225 nm, 60:40 EtOH/heptane at 1.0 mL/min,  $t_R$  = 5.55 min, 50% and  $t_R$  = 7.17 min, 50%; Anal. Calcd for  $C_{20}H_{25}N_3O_3 \cdot 0.2CH_2Cl_2 \cdot 0.2MeOH$ : C, 64.68; H, 6.97; N, 11.09. Found: C, 64.46; H, 6.84; N, 11.11.

## Example 451

## (±)-(cis)-6-{4-[2-(3-Hydroxycyclohexylamino)ethyl]phenoxy}nicotinamide

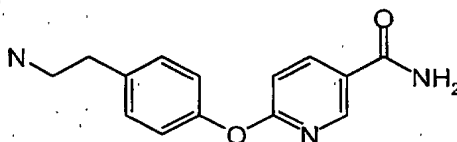
Part A: 3-(*tert*-Butyldimethylsilyloxy)cyclohexanone

Stir a mixture of 1,3-cyclohexanediol (250.9 mg, 2.16 mmol) and NaH (80% in mineral oil, 71.3 mg, 2.38 mmol) in freshly distilled THF (5.0 mL) for 30 minutes. Add *tert*-butyldimethylsilyl chloride (325.5 mg, 2.16 mmol) in THF (2.0 mL in total). Stir for 2 hours, add THF (3.0 mL) to the milky solution, and stir overnight. Quench the reaction with brine and extract with EtOAc (3 x 30 mL). Combine extracts, dry over  $MgSO_4$ , and

concentrate. Flash chromatography, eluting with 30% Et<sub>2</sub>O/hexanes yields a mono-silyl ether (185.5 mg, 37%).

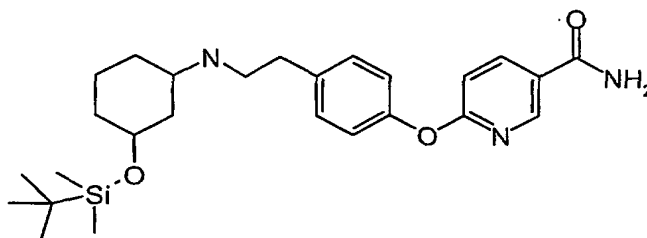
Add PCC (344 mg, 1.6 mmol) to the mono-protected cyclohexanediol (183.8 mg, 0.8 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at room temperature and stir overnight. Filter through a Celite® pad with thorough CH<sub>2</sub>Cl<sub>2</sub> rinse. Wash the filtrate with saturated aqueous NaHCO<sub>3</sub> and brine (30 mL each). Back-extract the aqueous layers with CH<sub>2</sub>Cl<sub>2</sub> (2 x 30 mL). Combine the organic layers, dry over MgSO<sub>4</sub>, concentrate and purify by flash chromatography, eluting with 20% Et<sub>2</sub>O/hexanes to afford the title compound (150.7 mg, 83%): HRMS calcd for C<sub>12</sub>H<sub>24</sub>O<sub>2</sub>NaSi 251.1443 (M+Na)<sup>+</sup>, found 251.1432, time 0.43 min; IR (cm<sup>-1</sup>) 1711 (C=O).

Part B: 6-[4-(2-Aminoethyl)phenoxy]nicotinamide



Treat [2-(4-hydroxyphenyl)ethyl]carbamic acid *tert*-butyl ester (534.3 mg, 2.2 mmol) with NaH (80% in mineral oil, 78.0 mg (2.6 mmol) in anhydrous DMF (10 mL) at room temperature for 30 minutes. Add 6-chloronicotinamide (343.8 mg, 2.2 mmol) and heat the mixture at 80 °C overnight. Quench the reaction with H<sub>2</sub>O and concentrate to dryness, using xylenes to remove DMF as an azeotrope. Suspend the residue in MeOH and filter with thorough MeOH and CH<sub>2</sub>Cl<sub>2</sub> rinse. Concentrate the filtrate and purify by flash chromatography, eluting with 75:15:10 EtOAc/CH<sub>2</sub>Cl<sub>2</sub>/2.0 M NH<sub>3</sub> in MeOH. Deprotect the BOC group with 1:1 TFA/ CH<sub>2</sub>Cl<sub>2</sub> (16 mL) at room temperature overnight. Concentrate and purify by an SCX column, washing with MeOH and then eluting with 2.0 M NH<sub>3</sub> in MeOH: MS ES<sup>+</sup> 297.9 (M+H+K)<sup>+</sup>, HRMS calcd for C<sub>14</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub> 258.1243 (M+H)<sup>+</sup>, found 258.1235, time 0.40 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 6.93 min, 100% purity.

Part C: ( $\pm$ )-(cis)- and (*trans*)-6-(4-{2-[3-(*tert*-Butyldimethylsilyloxy)cyclohexylamino]ethyl}phenoxy)nicotinamide



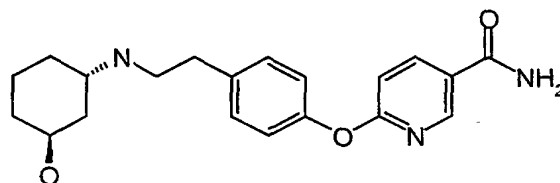
Dissolve 6-[4-(2-aminoethyl)phenoxy]nicotinamide (121.4 mg, 0.472 mmol) in MeOH (0.48 mL) and dichloroethane (1.0 mL). Add 3-(*tert*-butyldimethylsilyloxy)cyclohexanone (151 mg, 0.661 mmol) in dichloroethane (2.0 mL). Add the mixture to a solution of NaB(OAc)<sub>3</sub>H (140 mg, 0.661 mmol) in dichloroethane (1.3 mL). After 10 minutes, add dropwise AcOH (27  $\mu$ L, 0.472 mmol) and stir the mixture overnight. Quench the reaction with 1.0 N NaOH (4.0 mL) and take up the mixture in Et<sub>2</sub>O (30 mL). Separate the layers, and extract the aqueous layer with Et<sub>2</sub>O (3 x 20 mL). Wash the organic layers with brine (40 mL), dry over MgSO<sub>4</sub>, and concentrate. Purify by flash chromatography, eluting with 55:40:5 EtOAc/CH<sub>2</sub>Cl<sub>2</sub>/2.0 M NH<sub>3</sub> in MeOH to afford a diastereomeric mixture of the product (144.7 mg, 65%), which is separable by repeated flash chromatography, eluting with 5-10% 2.0 M NH<sub>3</sub> in MeOH/CH<sub>2</sub>Cl<sub>2</sub>: MS ES<sup>+</sup> 470.1 (M+H)<sup>+</sup>, ES<sup>-</sup> 468.2 (M-H)<sup>-</sup>.

Part D: ( $\pm$ )-(cis)-6-{4-[2-(3-Hydroxycyclohexylamino)ethyl]phenoxy}nicotinamide

Treat ( $\pm$ )-(cis)-6-(4-{2-[3-(*tert*-butyldimethylsilyloxy)cyclohexylamino]ethyl}phenoxy)nicotinamide (56.8 mg, 0.12 mmol) in THF (1.0 mL) with 1.0 M tetrabutylammonium fluoride (TBAF) in THF (0.5 eq) for 1 hour. Add another 0.5 eq of 1.0 M TBAF and stir for 4 hours. Add 1.0 eq of 1.0 M TBAF and stir for 2.5 days. Concentrate and purify by flash chromatography, eluting with 10% (2.0 M NH<sub>3</sub> in MeOH) in CH<sub>2</sub>Cl<sub>2</sub>. Repeat the chromatography to afford the title compound (29.9 mg, 70%): MS ES<sup>+</sup> 356.0 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>2</sub> 356.1974 (M+H)<sup>+</sup>, found 356.1965, time 0.41 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-99% over 19 min], t<sub>R</sub> = 7.11 min, 100% purity; Anal. Calcd for C<sub>20</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>·0.4CH<sub>2</sub>Cl<sub>2</sub>·0.4MeOH: C, 62.11; H, 6.87; N, 10.45. Found: C, 61.95; H, 6.88; N, 10.36.

**Example 452**

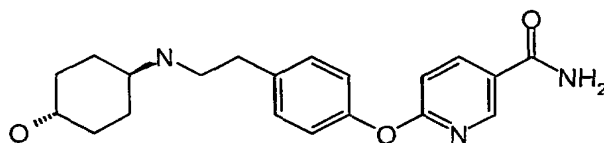
(±)-(trans)-6-{4-[2-(3-Hydroxycyclohexylamino)ethyl]phenoxy}nicotinamide



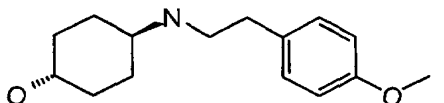
Treat (±)-(trans)-6-(4-{2-[3-(*tert*-butyldimethylsilyloxy)cyclohexylamino]ethyl}phenoxy)nicotinamide (Example 451, Part C, 63.3 mg, 0.13 mmol) in THF (1.0 mL) with 1.0 M tetrabutylammounium fluoride (TBAF) in THF (0.5 eq) for 1 hour. Add another 0.5 eq of 1.0 M TBAF and stir for 4 hours. Add 1.0 eq of 1.0 M TBAF and stir for 9 days. Add another 1.0 eq of 1.0 M TBAF and stir for 4 days. Concentrate, dissolve the mixture in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), and wash with H<sub>2</sub>O (2x 20 mL), saturated aqueous NaHCO<sub>3</sub> and brine (20 mL each). Back-extract the aqueous layers with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). Concentrate the two H<sub>2</sub>O washings and purify by flash chromatography, eluting with 15% (2.0 M NH<sub>3</sub> in MeOH) in CH<sub>2</sub>Cl<sub>2</sub> to afford the title compound (42.1 mg, 88%): MS ES<sup>+</sup> 356.4 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>2</sub> 356.1974 (M+H)<sup>+</sup>, found 356.1979, time 0.41 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-99% over 19 min], t<sub>R</sub> = 7.11 min, 100% purity.

**Example 453**

(±)-6-{4-[2-((trans)-4-Hydroxycyclohexylamino)ethyl]phenoxy}nicotinamide



## Part A: (±)-(trans)-4-[2-(4-Methoxyphenyl)ethylamino]cyclohexanol



Heat a mixture of (±)-(trans)-4-aminocyclohexanol (607 mg, 5.3 mmol),  $\text{Cs}_2\text{CO}_3$  (4.300 g, 13.2 mmol), and 1-(2-chloroethyl)-4-methoxybenzene (0.8 mL) in DMF (10 mL) at 100 °C for 19 hours. Quench the reaction with saturated aqueous  $\text{NH}_4\text{Cl}$  (40 mL). Adjust the pH to alkaline and concentrate to dryness. Suspend the residue in 50:40:10 EtOAc/ $\text{CH}_2\text{Cl}_2$ /2.0 M  $\text{NH}_3$  in MeOH and stir vigorously for 1 hour. Decant the supernatant. Suspend the residue in 10:90 2.0 M  $\text{NH}_3$  in MeOH/ $\text{CH}_2\text{Cl}_2$  for 30 minutes and filter. Combine the organic layers, concentrate, and purify by flash chromatography, eluting with 75:15:10 EtOAc/ $\text{CH}_2\text{Cl}_2$ /2.0 M  $\text{NH}_3$  in MeOH to afford the title compound (258.3 mg, 20%): MS  $\text{ES}^+$  250.0 ( $\text{M}+\text{H}$ ) $^+$ , HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), acetonitrile in water containing 0.01% concentrated HCl at 1.0 mL/min, 30-99% over 19 min],  $t_R$  = 1.96 min, 100% purity.

## Part B: (±)-6-{4-[2-((trans)-4-Hydroxycyclohexylamino)ethyl]phenoxy}nicotinamide

Add dropwise 1.0 M  $\text{BBr}_3$  in heptane (1.35 mL, 1.35 mmol) to a suspension of (±)-(trans)-4-[2-(4-methoxyphenyl)ethylamino]cyclohexanol (Part A, 153.2 mg, 0.61 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (5.0 mL) at 0 °C. Add another 1.0 mL of  $\text{CH}_2\text{Cl}_2$  when the compound precipitates out. Stir the mixture at 0 °C for 30 minutes and at room temperature for 2 hours. Quench the reaction with 5 drops of  $\text{H}_2\text{O}$  and concentrate. Purify the residue on an SCX column, washing with MeOH and then eluting with 2.0 M  $\text{NH}_3$  in MeOH to yield (±)-(trans)-4-[2-(4-hydroxycyclohexylamino)ethyl]phenol (121.2 mg).

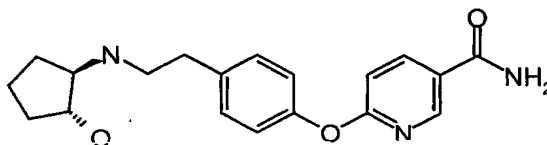
Heat a mixture of the phenol (121.2 mg, 0.52 mmol), 6-chloronicotinamide (121.0 mg, 0.77 mmol), and  $\text{K}_2\text{CO}_3$  (213.5 mg, 1.55 mmol) in 3:1 DMF/toluene (6.0 mL) at 165 °C for 3 hours. Quench the reaction with a small amount of  $\text{H}_2\text{O}$  and concentrate to dryness, using xylenes to remove DMF azeotropically. Dissolve the residue in MeOH and filter. Concentrate the filtrate and purify by flash chromatography, eluting with 75:15:10 EtOAc/ $\text{CH}_2\text{Cl}_2$ /2.0 M  $\text{NH}_3$  in MeOH, to afford the title compound (79.1 mg,



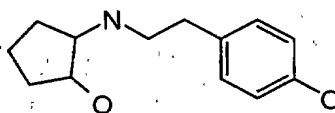
43%): MS ES<sup>+</sup> 356.0 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub> 356.1974 (M+H)<sup>+</sup>, found 356.1959, time 0.34 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), acetonitrile in water containing 0.01% concentrated HCl at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 5.81 min, 100% purity.

### Example 454

(±)-6-{4-[2-((*trans*)-2-Hydroxycyclopentylamino)ethyl]phenoxy}nicotinamide



Part A: 4-[2-(2-Hydroxycyclopentylamino)ethyl]phenol



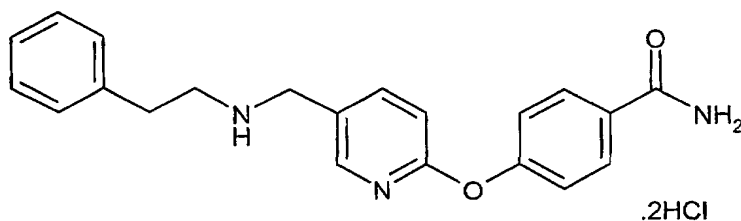
Stir a mixture of cyclopentene oxide (482.0 mg, 5.73 mmol) and tyramine (943.2 mg, 6.88 mmol) in 1.0 N NaOH (20 mL) at room temperature for 64 hours, at 45-55 °C for 6 hours, and at 100 °C for 18 hours. Quench the reaction with saturated aqueous NH<sub>4</sub>Cl (40 mL) and take it up in EtOAc (50 mL). Separate the layers after shaking. Wash the organic layer with H<sub>2</sub>O and brine (50 mL each). Back-extract the aqueous layers with CH<sub>2</sub>Cl<sub>2</sub>, EtOAc and CH<sub>2</sub>Cl<sub>2</sub> (50 mL each). Adjust the pH of the combined aqueous layers to alkaline and concentrate. Suspend the residue in 10:40:50 2.0 M NH<sub>3</sub> in MeOH/CH<sub>2</sub>Cl<sub>2</sub>/EtOAc and decant off the supernatant. Dissolve the residual solid in H<sub>2</sub>O and extract it with 10:40:50 2.0 M NH<sub>3</sub> in MeOH/CH<sub>2</sub>Cl<sub>2</sub>/EtOAc (100 mL) and 10:90 2.0 M NH<sub>3</sub> in MeOH/CH<sub>2</sub>Cl<sub>2</sub>. Combine all the organic layers and concentrate. Dissolve the residue in a small amount of MeOH and purify by flash chromatography, eluting with 10:40:50 2.0 M NH<sub>3</sub> in MeOH/CH<sub>2</sub>Cl<sub>2</sub>/EtOAc to afford the title compound as a 1:3 *cis/trans* isomeric mixture (566 mg, 45%): MS ES<sup>+</sup> 222.0 (M+H)<sup>+</sup>, HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), acetonitrile in water containing 0.01% concentrated HCl at 1.0 mL/min, 5-95% over 19 min], t<sub>R</sub> = 4.72 min, 76% and 6.52 min, 24%.

Part B: (±)-6-{4-[2-((*trans*)-2-Hydroxycyclopentylamino)ethyl]phenoxy}nicotinamide

Heat a mixture of 4-[2-(2-hydroxycyclopentylamino)ethyl]phenol (210.5 mg, 0.95 mmol),  $K_2CO_3$  (395 mg, 2.85 mmol) and 6-chloronicotinamide (223.4 mg, 1.43 mmol) in 1:3 toluene/DMF (6 mL) at 165 °C for 2 hours, while removing  $H_2O$  azeotropically with toluene. Remove DMF azeotropically with xylenes and take up the residue in  $H_2O$  (50 mL) and 10% MeOH in  $CH_2Cl_2$  (50 mL). Shake and separate the layers. Extract the aqueous layer with 10% MeOH in  $CH_2Cl_2$  (2 x 50 mL) and 10% MeOH in EtOAc (50 mL). Combine the organic layers, dry over  $MgSO_4$  and concentrate. Concentrate the aqueous layer, which still contains the product by TLC, to dryness and extract the product out with MeOH. Dry the solution with  $Na_2SO_4$ , filter and combine with the organic concentrate above. Concentrate, re-dissolve in MeOH and filter through a  $Na_2SO_4$  pad. Concentrate and purify by flash chromatography, eluting with 10:15:75 2.0 M  $NH_3$  in MeOH/ $CH_2Cl_2$ /EtOAc to afford the title compound (137.4 mg) along with the (*cis*)-isomer of the starting phenol (59.0 mg) recovered: MS  $ES^+$  342.0 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{19}H_{24}N_3O_3$  342.1818 ( $M+H$ ) $^+$ , found 342.1812, time 0.34 min; HPLC [YMC-Pack Pro C-18 (150 x 4.6 mm, S-5 microm), acetonitrile in water containing 0.01% concentrated HCl at 1.0 mL/min, 5-95% over 19 min],  $t_R$  = 16.76 min, 100% purity; Anal. Calcd for  $C_{19}H_{23}N_3O_3 \cdot 0.1CH_2Cl_2 \cdot 0.1EtOAc$ : C, 65.29; H, 6.74; N, 11.71. Found: C, 65.35; H, 6.61; N, 11.98.

#### Example 455

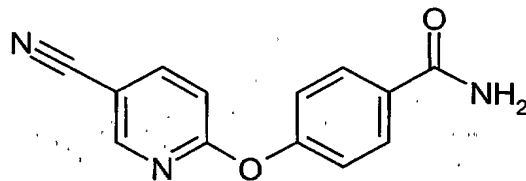
4-[5-(Phenethylamino-methyl)-pyridin-2-yloxy]-benzamide dihydrochloride



303

## Step 1

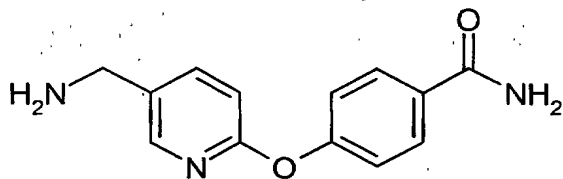
## 4-(5-Cyano-pyridin-2-yloxy)-benzamide



Combine 6-chloro-nicotinonitrile (1.0 g, 7.22 mmol), 4-hydroxybenzamide (1.09 g, 7.94 mmol), and potassium carbonate (1.49 g, 10.83 mmol) in toluene (8 mL). Add DMA (24 mL) to the reaction mixture. Heat the reaction mixture for 1.5 hour at 120 °C. Let the reaction mixture cool to room temperature. Pour the reaction mixture onto water and filter the precipitate washing with water. Dry the solid under vacuum to provide the title compound (1.63 g, 94%)

## Step 2

## 4-(5-Aminomethyl-pyridin-2-yloxy)-benzamide



Combine 4-(5-cyano-pyridin-2-yloxy)-benzamide (202 mg, 0.844 mmol), 5% Pd/C (80 mg) and conc. HCl (0.423 mL) in THF (4 mL) and EtOH (4 mL). Run the reaction under hydrogen atmosphere (1 atm) at rt overnight. Add NaOH (5 N, 2 mL) and filter the reaction mixture through Celite®. Concentrate the filtrate. Wash the residue with H<sub>2</sub>O (5 mL) and extract with CH<sub>2</sub>Cl<sub>2</sub> (3x5 mL). Combine the organic layers and purify through an SCX column eluting with 2M ammonia in methanol. Concentrate the fractions to give the title compound (74 mg, 36%).

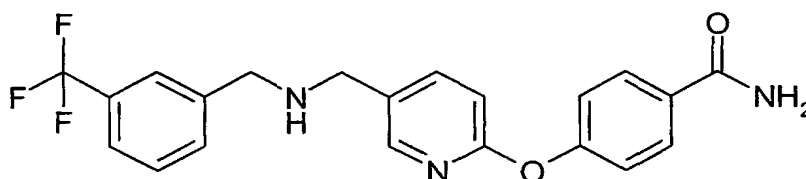
## Step 3

Combine 4-(5-aminomethyl-pyridin-2-yloxy)-benzamide (70 mg, 0.288 mmol) from step 2, methanol (1.8 mL), trimethylorthoformate (1.2 mL), and phenethyl aldehyde (0.034 mL, 0.288 mmol). Stir at room temperature for 4 hours, then add sodium

borohydride (13 mg, 0.346 mmol). Stir for 4h. Purify through an SCX column using ammonia (2.0 M in methanol) to give 20 mg (20%) of the free base. Combine the compound with ether (1 mL) and hydrochloric acid (1 M in ether). Triturate and filtrate to give 24 mg of the title compound. Mass spectrum (ion spray):  $m/z = 348.0$  (M+1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.02 (d,  $J = 1.8$  Hz, 1H), 7.77 (d,  $J = 8.6$  Hz, 2H), 7.62 (dd,  $J = 2.1$  Hz, 8.6 Hz, 1H), 7.25-7.19 (m, 2H), 7.16-7.08 (m, 5H), 6.85 (d,  $J = 8.3$  Hz, 1H), 6.18-5.72 (bm, 2H), 3.69 (s, 2H), 2.83 (t,  $J = 6.4$  Hz, 2H), 2.75 (t,  $J = 6.4$  Hz, 2H), 1.85-1.51 (bs, 1H).

### Example 456

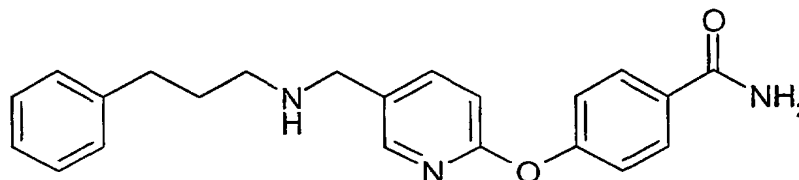
4-{5-[(3-Trifluoromethyl-benzylamino)-methyl]-pyridin-2-yloxy}-benzamide



Using a method similar to Example 455, step 3, using 3-trifluoro-benzaldehyde (0.045 mL, 0.339 mmol) gives the title compound (106 mg, 85%). Mass spectrum (ion spray):  $m/z = 401.9$  (M+1);  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ): 8.08 (d,  $J = 2.4$  Hz, 1H), 7.97-7.93 (bs, 1H), 7.90 (d,  $J = 8.7$  Hz, 2H), 7.85 (dd,  $J = 2.4$  Hz, 8.5 Hz, 1H), 7.69 (s, 1H), 7.63 (d,  $J = 7.6$  Hz, 1H), 7.58-7.50 (m, 2H), 7.33 (s, 1H), 7.12 (d,  $J = 8.7$  Hz, 2H), 7.03 (d,  $J = 8.5$  Hz, 1H), 3.76 (s, 2H), 3.66 (s, 2H).

### Example 457

4-{5-[(3-Phenyl-propylamino)-methyl]-pyridin-2-yloxy}-benzamide

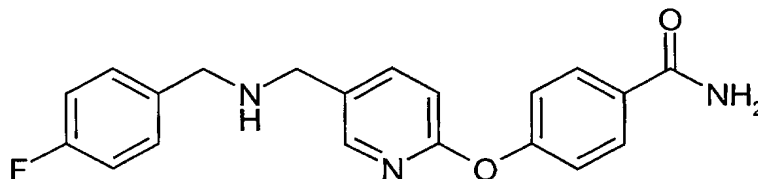


Using a method similar to Example 455, step 3, using 3-phenyl-propyl-aldehyde (0.045 mL, 0.339 mmol) gives the title compound (45 mg, 41%). Mass spectrum (ion spray):  $m/z = 361.9$  (M+1);  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ): 8.07 (d,  $J = 2.1$  Hz, 1H), 7.94 (bs, 1H), 7.90 (d,  $J = 8.7$  Hz, 2H), 7.82 (dd,  $J = 2.5$  Hz, 8.3 Hz, 1H), 7.33 (bs, 1H), 7.24 (t,  $J = 7.4$

Hz, 2H), 7.17-7.11 (m, 5H), 7.02 (d,  $J = 8.3$  Hz, 1H), 3.64 (s, 2H), 2.58 (t,  $J = 7.6$  Hz, 2H), 2.46 (t,  $J = 7.6$  Hz, 2H), 1.69 (quintet,  $J = 7.6$  Hz, 2H).

#### Example 458

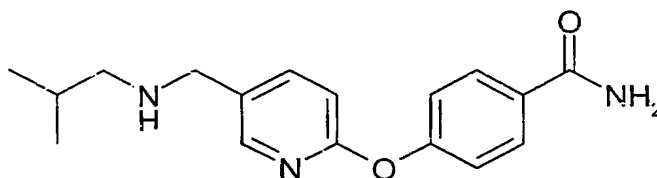
4-{5-[(4-Fluoro-benzylamino)-methyl]-pyridin-2-yloxy}-benzamide



Using a method similar to Example 455, step 3, using 4-fluoro-benzaldehyde (0.036 mL, 0.339 mmol) gives the title compound (97 mg, 90%). Mass spectrum (ion spray):  $m/z = 351.9$  ( $M+1$ );  $^1\text{H}$  NMR (DMSO- $d_6$ ): 8.07 (d,  $J = 2.3$  Hz, 1H), 7.95 (bs, 1H), 7.90 (d,  $J = 9.0$  Hz, 2H), 7.84 (dd,  $J = 2.5$  Hz, 8.4 Hz, 1H), 7.37-7.32 (m, 3H), 7.14-7.08 (m, 4H), 7.03 (d,  $J = 8.6$  Hz, 1H), 3.64 (s, 2H), 3.63 (s, 2H).

#### Example 459

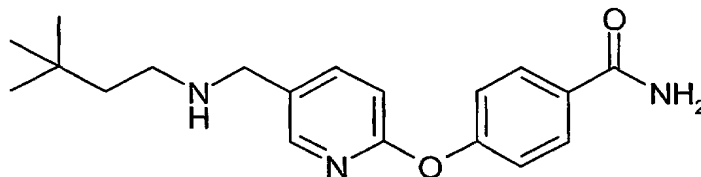
4-[5-(Isobutylamino-methyl)-pyridin-2-yloxy]-benzamide



Using a method similar to Example 455, step 3, using isobutylaldehyde (0.031 mL, 0.339 mmol) gives the title compound (71 mg, 77%). Mass spectrum (ion spray):  $m/z = 300.0$  ( $M+1$ );  $^1\text{H}$  NMR (DMSO- $d_6$ ): 8.07 (d,  $J = 2.4$  Hz, 1H), 7.94 (bs, 1H), 7.89 (d,  $J = 8.7$  Hz, 2H), 7.82 (dd,  $J = 2.4$  Hz, 8.2 Hz, 1H), 7.32 (bs, 1H), 7.12 (d,  $J = 8.7$  Hz, 2H), 7.03 (d,  $J = 8.2$  Hz, 1H), 3.64 (s, 2H), 2.26 (d,  $J = 6.6$  Hz, 2H), 1.64 (septet,  $J = 6.6$  Hz, 1H), 0.84 (d,  $J = 6.6$  Hz, 6H).

**Example 460**

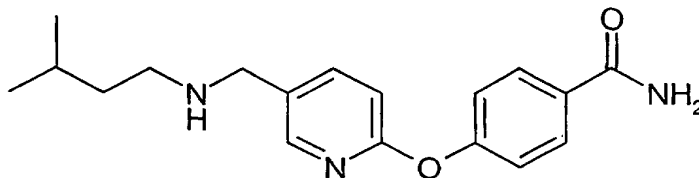
4-{5-[(3,3-Dimethyl-butylamino)-methyl]-pyridin-2-yloxy}-



Using a method similar to Example 455, step 3, using 3,3-dimethyl-butylaldehyde (0.062 mL, 0.493 mmol) gives the title compound (111 mg, 82%). Mass spectrum (ion spray):  $m/z = 327.9$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 8.06 (d,  $J = 2.5$  Hz, 1H), 7.93 (bs, 1H), 7.88 (d,  $J = 8.5$  Hz, 2H), 7.81 (dd,  $J = 2.5$  Hz, 8.5 Hz, 1H), 7.31 (bs, 1H), 7.11 (d,  $J = 8.5$  Hz, 2H), 7.02 (d,  $J = 8.5$  Hz, 1H), 3.63 (s, 2H), 2.46 (t,  $J = 8.7$  Hz, 2H), 1.98 (bs, 1H), 1.33 (t,  $J = 8.7$  Hz, 2H), 0.84 (s, 9H).

**Example 461**

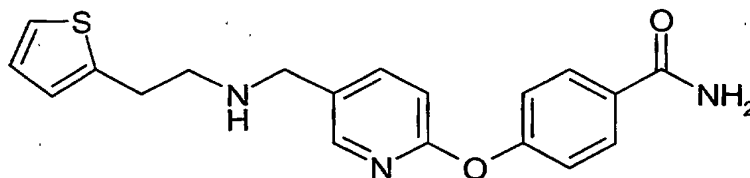
4-{5-[(3-Methyl-butylamino)-methyl]-pyridin-2-yloxy}-benzamide



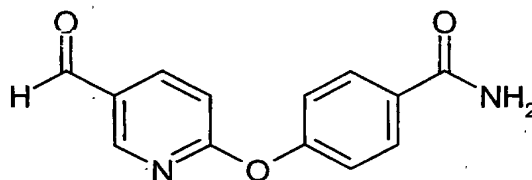
Using a method similar to Example 455, step 3, using 3-methyl-butylaldehyde (0.053 mL, 0.493 mmol) gives the title compound (102 mg, 79%). Mass spectrum (ion spray):  $m/z = 313.9$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 8.06 (d,  $J = 2.5$  Hz, 1H), 7.93 (bs, 1H), 7.88 (d,  $J = 8.7$  Hz, 2H), 7.81 (dd,  $J = 2.5$  Hz, 8.4 Hz, 1H), 7.31 (bs, 1H), 7.11 (d,  $J = 8.7$  Hz, 2H), 7.02 (d,  $J = 8.4$  Hz, 1H), 3.63 (s, 2H), 2.45 (t,  $J = 7.3$  Hz, 2H), 2.02 (bs, 1H), 1.59 (septet,  $J = 6.7$  Hz, 1H), 1.28 (q,  $J = 6.9$  Hz, 2H), 0.82 (d,  $J = 6.7$  Hz, 6H).

**Example 462**

4-{5-[(2-Thiophen-2-yl-ethylamino)-methyl]-pyridin-2-yloxy}-benzamide

**Step 1**

4-(5-Formyl-pyridin-2-yloxy)-benzamide



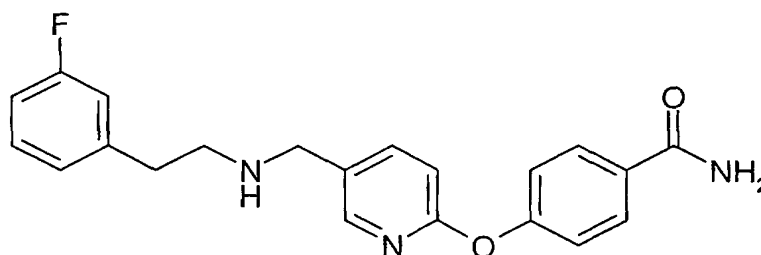
Combine 4-(5-cyano-pyridin-2-yloxy)-benzamide (501 mg, 2.09 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at  $0^\circ\text{C}$  with DIBAL-H (1.0 M in hexanes, 4.2 mL) dropwise. Stir the reaction mixture for 5 h. Pour the reaction mixture onto aqueous  $\text{NH}_4\text{Cl}$  and let stir overnight. Filter and redissolve in  $\text{CHCl}_3/\text{iPrOH}$  (3:1, 10 mL) and wash with NaOH (1 N, 7 mL). Extract the organic layer, dry over magnesium sulfate, filter and dry under vacuum to provide 4-(5-formyl-pyridin-2-yloxy)-benzamide (312 mg, 62%).

**Step 2**

Using a method similar to Example 455, step 3, using 2-thiophen-2-yl-ethylamine (0.027 mL, 0.227 mmol) and 4-(5-formyl-pyridin-2-yloxy)-benzamide (58 mg, 0.239 mmol) from step 1 (above) gives the title compound (23 mg, 27%). Mass spectrum (ion spray):  $m/z = 353.9$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 8.08 (d,  $J = 2.1$  Hz, 1H), 7.93 (bs, 1H), 7.89 (d,  $J = 8.7$  Hz, 2H), 7.82 (dd,  $J = 2.3$  Hz, 8.3 Hz, 1H), 7.31 (bs, 1H), 7.27 (dd,  $J = 1.0$  Hz, 5.2 Hz, 1H), 7.12 (d,  $J = 8.7$  Hz, 2H), 7.02 (d,  $J = 8.3$  Hz, 1H), 6.90 (dd,  $J = 3.5$  Hz, 5.2 Hz, 1H), 6.84 (d,  $J = 3.3$  Hz, 1H), 3.68 (s, 2H), 2.91 (t,  $J = 7.1$  Hz, 2H), 2.72 (t,  $J = 7.1$  Hz, 2H), 2.25 (bs, N-H).

**Example 463**

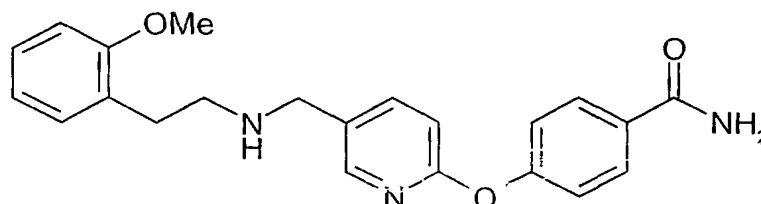
4-(5-{[2-(3-Fluoro-phenyl)-ethylamino]-methyl}-pyridin-2-yloxy)-benzamide



Using a method similar to example 462, step 2, using 3-fluoro-phenyl)-ethylamine (0.026 mL, 0.2 mmol) gives the title compound (14 mg, 18%) Mass spectrum (ion spray):  $m/z = 365.9$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 8.06 (bs, 1H), 7.93 (bs, 1H), 7.88 (d,  $J = 8.6$  Hz, 2H), 7.79 (d,  $J = 8.2$  Hz, 1H), 7.32-7.24 (m, 2H), 7.11 (d,  $J = 8.2$  Hz, 2H), 7.05-6.93 (m, 5H), 3.67 (s, 2H), 2.76-2.64 (m, 4H).

**Example 464**

4-(5-{[2-(2-Methoxy-phenyl)-ethylamino]-methyl}-pyridin-2-yloxy)-benzamide

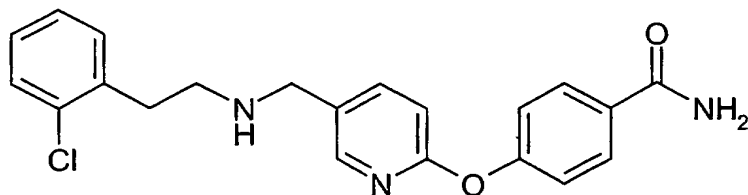


Using a method similar to example 462, step 2, using 2-methoxy-phenyl)-ethylamine (0.033 mL, 0.223 mmol) gives the title compound (48 mg, 57%). Mass spectrum (ion spray):  $m/z = 377.9$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 8.06 (d,  $J = 2.1$  Hz, 1H), 7.93 (bs, 1H), 7.89 (d,  $J = 8.6$  Hz, 2H), 7.79 (dd,  $J = 2.4$  Hz, 8.2 Hz, 1H), 7.31 (bs, 1H), 7.17-7.09 (m, 4H), 7.01 (d,  $J = 8.4$  Hz, 1H), 6.90 (d,  $J = 8.1$  Hz, 1H), 6.82 (t,  $J = 7.5$  Hz, 1H), 3.73 (s, 3H), 3.66 (s, 2H), 2.71-2.60 (m, 4H), 2.16 (bs, N-H).



**Example 465**

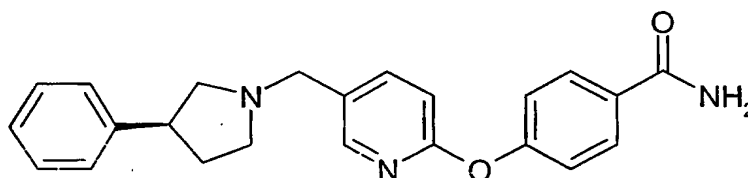
4-(5-{[2-(2-Chloro-phenyl)-ethylamino]-methyl}-pyridin-2-yloxy)-benzamide



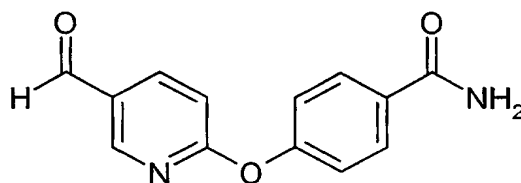
Using a method similar to example 462, step 2, using 2-chloro-phenyl)-ethylamine (0.028 mL, 0.198 mmol) gives the title compound (42 mg, 55%). Mass spectrum (ion spray):  $m/z$  = 381.8 ( $M+1$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 8.06 (bs, 1H), 7.93 (bs, 1H), 7.88 (d,  $J$  = 8.7 Hz, 2H), 7.80 (d,  $J$  = 8.3 Hz, 1H), 7.40-7.29 (m, 3H), 7.26-7.17 (m, 2H), 7.11 (d,  $J$  = 8.3 Hz, 2H), 7.01 (d,  $J$  = 8.3 Hz, 1H), 3.68 (s, 2H), 2.82 (t,  $J$  = 6.6 Hz, 2H), 2.68 (t,  $J$  = 6.6 Hz, 2H), 2.27 (bs, N-H).

**Example 466**

(+)-4-[5-(3-Phenyl-pyrrolidin-1-ylmethyl)-pyridin-2-yloxy]-benzamide

**Step 1**

4-(5-Formyl-pyridin-2-yloxy)-benzamide



Combine 4-(5-cyano-pyridin-2-yloxy)-benzamide (501 mg, 2.09 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at 0 °C with DIBAL-H (1.0 M in hexanes, 4.2 mL) dropwise. Stir the reaction mixture for 5 h. Pour the reaction mixture onto aqueous  $\text{NH}_4\text{Cl}$  and let stir overnight.

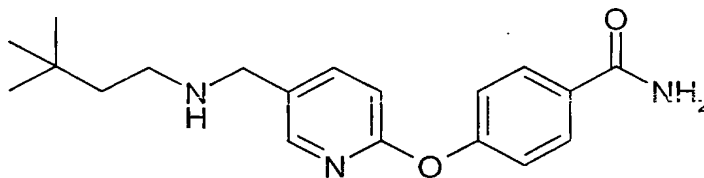
Filter and redissolve in  $\text{CHCl}_3/\text{iPrOH}$  (3:1, 10 mL) and wash with NaOH (1 N, 7 mL). Extract the organic layer, dry over magnesium sulfate, filter and dry under vacuum to provide 4-(5-formyl-pyridin-2-yloxy)-benzamide (312 mg, 62%).

### Step 2

Combine 4-(5-formyl-pyridin-2-yloxy)-benzamide (100 mg, 0.413 mmol), (+)-3-phenyl-pyrrolidine (78 mg, 0.318 mmol), sodium triacetoxy-borohydride (101 mg, 0.477 mmol), AcOH (0.018 mL, 0.318 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL). Stir at rt overnight. Pour the reaction mixture onto an SCX column, eluting with ammonia (2M in methanol) followed by chromatography [ $\text{CH}_2\text{Cl}_2$ :ammonia (2.0 M in methanol) 20:1] to provide the title compound (43 mg, 36%). Mass spectrum (ion spray):  $m/z = 373.9$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ): 8.09 (d,  $J = 1.9$  Hz, 1H), 7.93 (bs, 1H), 7.89 (d,  $J = 8.6$  Hz, 2H), 7.82 (dd,  $J = 2.2$  Hz, 8.6 Hz, 1H), 7.30 (bs, 1H), 7.27-7.24 (m, 4H), 7.17-7.12 (m, 3H), 7.03 (d,  $J = 8.3$  Hz, 1H), 3.61 (dd,  $J = 13.1$  Hz, 19.5 Hz, 2H), 3.33-3.24 (m, 1H), 2.88 (t,  $J = 8.3$  Hz, 1H), 2.66 (t,  $J = 7.0$  Hz, 2H), 2.42 (t,  $J = 8.3$  Hz, 1H), 2.28-2.18 (m, 1H), 1.79-1.70 (m, 1H).

### Example 467

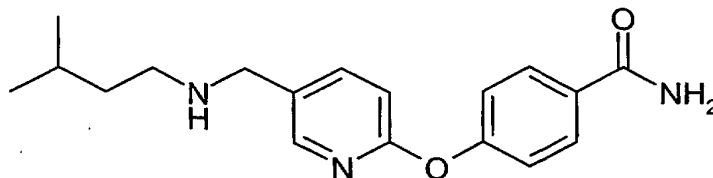
4-{5-[(3,3-Dimethyl-butylamino)-methyl]-pyridin-2-yloxy}-benzamide



The title compound is prepared following the procedure of Example 462 using the corresponding amine. Mass spectrum (ion spray):  $m/z = 327.9$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ): 8.06 (d,  $J = 2.5$  Hz, 1H), 7.93 (bs, 1H), 7.88 (d,  $J = 8.5$  Hz, 2H), 7.81 (dd,  $J = 2.5$  Hz, 8.5 Hz, 1H), 7.31 (bs, 1H), 7.11 (d,  $J = 8.5$  Hz, 2H), 7.02 (d,  $J = 8.5$  Hz, 1H), 3.63 (s, 2H), 2.46 (t,  $J = 8.7$  Hz, 2H), 1.98 (bs, 1H), 1.33 (t,  $J = 8.7$  Hz, 2H), 0.84 (s, 9H).

**Example 468**

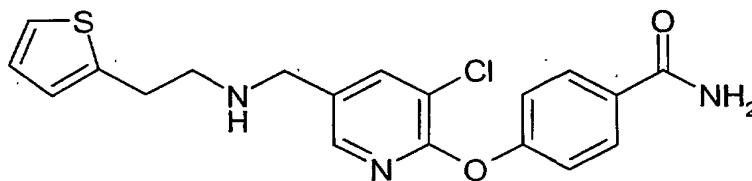
4-{5-[(3-Methyl-butylamino)-methyl]-pyridin-2-yloxy}-benzamide



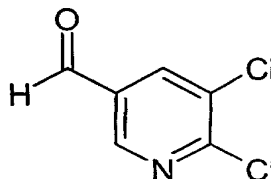
The title compound is prepared following the method of Example 455, step 3 using the corresponding amine. Mass spectrum (ion spray):  $m/z = 313.9$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 8.06 (d,  $J = 2.5$  Hz, 1H), 7.93 (bs, 1H), 7.88 (d,  $J = 8.7$  Hz, 2H), 7.81 (dd,  $J = 2.5$  Hz, 8.4 Hz, 1H), 7.31 (bs, 1H), 7.11 (d,  $J = 8.7$  Hz, 2H), 7.02 (d,  $J = 8.4$  Hz, 1H), 3.63 (s, 2H), 2.45 (t,  $J = 7.3$  Hz, 2H), 2.02 (bs, 1H), 1.59 (septet,  $J = 6.7$  Hz, 1H), 1.28 (q,  $J = 6.9$  Hz, 2H), 0.82 (d,  $J = 6.7$  Hz, 6H).

**Example 469**

4-{3-Chloro-5-[(2-thiophen-2-yl-ethylamino)-methyl]-pyridin-2-yloxy}-benzamide

**Step 1**

5,6-Dichloro-pyridine-3-carbaldehyde

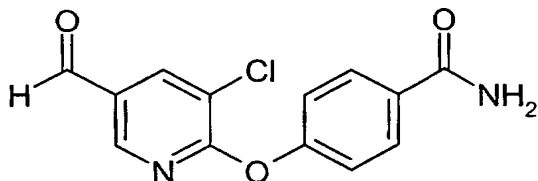


Combine (5,6-dichloro-pyridin-3-yl)-methanol (3.05 g, 17.11 mmol) and manganese dioxide (37.2 g, 427.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (25 mL). Stir the reaction mixture at rt overnight. Filter the reaction mixture through Celite® washing with  $\text{CH}_2\text{Cl}_2$  (2x10 mL).

Concentrate the filtrate and dry under vacuum to provide the title compound (1.44 g, 48%).

### Step 2

#### 4-(3-Chloro-5-formyl-pyridin-2-yloxy)-benzamide



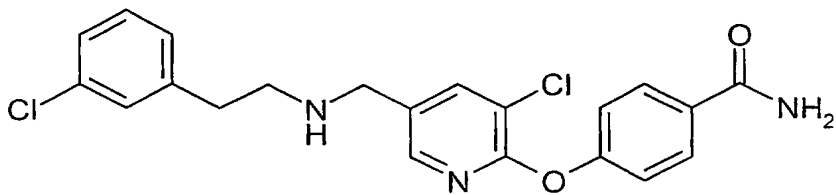
Combine 5,6-dichloro-pyridine-3-carbaldehyde (1.37 g, 7.80 mmol), 4-hydroxy-benzamide (1.18 g, 8.58 mmol), potassium carbonate (1.62 g, 11.7 mmol) in toluene (10 mL) and DMA (30 mL). Stir the reaction mixture at 100 °C for 1 h. Pour the reaction mixture onto H<sub>2</sub>O (100 mL) and extract with Et<sub>2</sub>O (100 mL). Wash the organic layer with H<sub>2</sub>O (2x100 mL), dry the organic phase extracts over magnesium sulfate, filter and concentrate to give the title compound (1.09 g, 51%).

### Step 3

Using a method similar to Example 460, using 4-(3-chloro-5-formyl-pyridin-2-yloxy)-benzamide (114 mg, 0.412 mmol) and 2-thiophen-2-yl-ethylamine (0.048 mL, 0.412 mmol) gives the title compound (57 mg, 35%). Mass spectrum (ion spray):  $m/z$  = 387.9 (M+1); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 8.37 (bs, 1H), 8.21 (d,  $J$  = 1.9 Hz, 1H), 7.99 (bs, 1H), 7.93 (d,  $J$  = 8.7 Hz, 2H), 7.39 (dd,  $J$  = 1.2 Hz, 5.0 Hz, 1H), 7.36 (bs, 1H), 7.21 (d,  $J$  = 8.9 Hz, 2H), 6.99-6.94 (m, 2H), 4.16 (s, 2H), 3.26-3.11 (m, 4H).

### Example 470

#### 4-(3-Chloro-5-{[2-(3-chloro-phenyl)-ethylamino]-methyl}-pyridin-2-yloxy)-benzamide



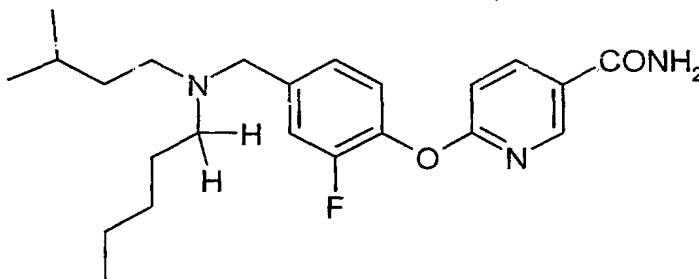
Using a method similar to Example 462, using 4-(3-chloro-5-formyl-pyridin-2-yloxy)-benzamide (101 mg, 0.365 mmol) and 2-(3-chloro-phenyl)-ethylamine (0.056 mL, 0.402 mmol) gives the title compound (57 mg, 36%). Mass spectrum (ion spray):  $m/z$  = 415.9 (M+1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.93 (d,  $J$  = 1.7 Hz, 1H), 7.86 (d,  $J$  = 8.7 Hz, 2H), 7.77 (d,  $J$  = 1.7 Hz, 1H), 7.22-7.17 (m, 4H), 7.07 (d,  $J$  = 7.0 Hz, 1H), 6.12 (bs, 2H), 3.74 (s, 2H), 2.87 (t,  $J$  = 6.8 Hz, 2H), 2.78 (t,  $J$  = 6.8 Hz, 2H), 1.42 (bs, 1H).

#### General Procedure for Examples 471-474

To a mixture of amine (1 equiv), aldehyde (1.5 equiv) in 5% AcOH/methanol (0.2 M) was added  $\text{NaCNBH}_4$  (5 equiv) and the resulting reaction mixture was stirred for 2 hours under nitrogen atmosphere at room temperature. The reaction can be monitored by electrospray MS or TLC. Ethyl acetate was added to the reaction mixture and washed twice with saturated aqueous solution of  $\text{NaHCO}_3$ . The organic layer was separated, dried over anhydrous  $\text{NaSO}_4$  and the solvent was evaporated to yield a residue which was purified by flash chromatography using chloroform/ethanol/ $\text{NH}_4\text{OH}$ , 94.5/5/0.5) to afford the title compound as a white solid.

#### **Example 471**

6-[2-Fluoro-4-((3-methyl-butyl) pentylaminomethyl)phenoxy]nicotinamide



Reductive amination of N-pentyl-N-3-methylbutylamine and 6-(2-fluoro-4-formyl-phenoxy)-nicotinamide as described above afforded the title compound in 86% yield.

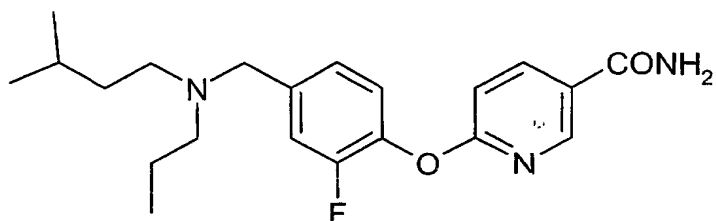
$^1\text{H}$  NMR ( $\text{CHCl}_3\text{-}d_3$ )  $\delta$ : 8.56 (d, 1H,  $J$  = 2.4 Hz), 8.17 (dd, 1H,  $J$  = 8.5, 2.4 Hz), 7.28-7.10 (m, 3H), 7.02 (d, 1H,  $J$  = 8.7 Hz), 6.21 (bs, 2H), 3.54 (s, 2H), 2.42 (dt, 4H,  $J$  = 8.7 Hz), 1.65-1.53 (m, 1H), 1.53-1.40 (m, 2H), 1.40-1.20 (m, 6H), 0.86 (t, 3H,  $J$  = 7.0 Hz), 0.85 (d, 6H,  $J$  = 6.5 Hz).

$^{13}\text{C}$  NMR ( $\text{CHCl}_3-d_3$ )  $\delta$ : 167.6, 165.5, 156.4, 153.1, 147.4, 139.7, 124.8, 123.5, 117.3, 117.1, 111.0, 58.2, 54.2, 52.3, 36.3, 30.0, 27.0, 26.6, 23.1, 23.0, 14.5.

MS (Electrospray): 402.2 ( $\text{M}^++1$ ).

#### Example 472

6-[2-Fluoro-4-((3-methyl-butylpropylamino)methyl)phenoxy]nicotinonamide



The title compound was prepared by reductive amination of 6-[2-fluoro-4-((3-methyl-butyl) aminomethyl)phenoxy]nicotinamide with propanaldehyde in 86% Yield.

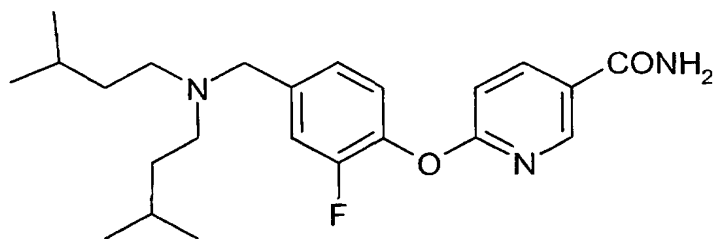
$^1\text{H}$  NMR ( $\text{CHCl}_3-d_3$ )  $\delta$ : 8.56 (d, 1H,  $J = 2.4$  Hz), 8.17 (dd, 1H,  $J = 8.5, 2.4$  Hz), 7.28-7.10 (m, 3H), 7.02 (d, 1H,  $J = 8.5$  Hz), 6.24 (bs, 2H), 3.54 (s, 2H), 1.65-1.55 (m, 1H), 1.55-1.40 (m, 2H), 1.40-1.30 (m, 2H), 0.86 (t, 3H,  $J = 7.0$  Hz), 0.85 (d, 6H,  $J = 6.5$  Hz).

$^{13}\text{C}$  NMR ( $\text{CHCl}_3-d_3$ )  $\delta$ : 167.6, 165.5, 156.4, 153.1, 147.5, 139.7, 124.8, 123.5, 117.3, 117.1, 111.0, 58.2, 56.3, 52.3, 36.3, 26.6, 23.1, 20.6, 12.3.

MS (Electrospray): 374.2 ( $\text{M}^++1$ ).

#### Example 473

6-[4-Bis-((3-methyl-butylamino)-methyl)-2-fluorophenoxy]nicotinonamide



The title compound was prepared by reductive amination of 6-[2-fluoro-4-((3-methyl-butyl) aminomethyl)phenoxy]nicotinamide with 3-methylbutanaldehyde in 80% Yield.

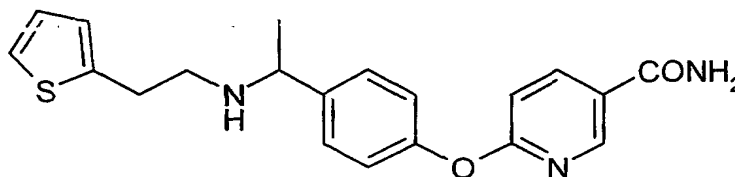
$^1\text{H}$  NMR ( $\text{CHCl}_3\text{-}d_3$ )  $\delta$ : 8.55 (d, 1H,  $J = 2.4$  Hz), 8.17 (dd, 1H,  $J = 8.5, 2.4$  Hz), 7.28-7.10 (m, 3H), 7.02 (d, 1H,  $J = 8.7$  Hz), 6.25 (bs, 2H), 3.53 (s, 2H), 2.44 (t, 4H,  $J = 7.3$  Hz), 1.58 (sept, 2H,  $J = 7.3$  Hz), 1.35 (dt, 4H,  $J = 7.3$  Hz), 0.85 (dd, 6H,  $J = 6.7$  Hz).

$^{13}\text{C}$  NMR ( $\text{CHCl}_3\text{-}d_3$ )  $\delta$ : 167.6, 165.5, 156.4, 153.1, 147.5, 139.7, 124.8, 123.5, 117.4, 117.1, 111.0, 58.2, 52.3, 36.3, 26.6, 23.1.

MS (Electrospray): 402.2 ( $\text{M}^+ + 1$ ).

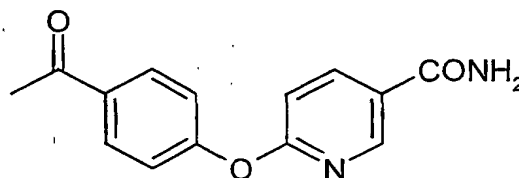
#### Example 474

6-[4-1-(2-Thiophen-2-ylethylaminoethyl)-phenoxy]nicotinamide



#### Step 1

(4-Acetyl-phenoxy) nicotinamide



4-Hydroxyacetophenone (1 equiv), 6-chloronicotinamide (1 equiv) and  $\text{K}_2\text{CO}_3$  (1.4 equiv) in anhydrous DMF (0.4 M) was heated at 150 °C under nitrogen during 2.5 days. After cooling down to room temperature, toluene was added and solvents were evaporated. The residue was partitioned in water/EtOAc. The aqueous layer was thoroughly extracted with EtOAc. The combined organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum (toluene was added to aid DMF evaporation). The crude mixture was purified by flash chromatography using EtOAc/ $\text{CH}_2\text{Cl}_2$ /2 M  $\text{NH}_3$  in MeOH (12:7:1) as eluent in 20% yield.

$^1\text{H}$  NMR ( $\text{MeOH-}d_4$ )  $\delta$ : 8.63 (d, 1H,  $J = 2.7$  Hz), 8.30 (dd, 1H,  $J = 8.6, 2.7$  Hz), 8.06 and 7.25 (AA'BB' system, 4H), 7.10 (d, 1H,  $J = 8.6$  Hz), 2.61 (s, 3H)

$^{13}\text{C}$  NMR (MeOH- $d_4$ )  $\delta$ : 196.2, 165.1, 163.4, 156.8, 146.9, 139.2, 132.9, 129.7, 125.3, 120.6, 110.8, 26.1

MS (Electrospray): 257.0 ( $\text{M}^+ + 1$ ).

#### Step 2

To a mixture of the ketone (step 1) (1 equiv) and 2-thiophen-2-ylethylamine (1.5 equiv), in THF (0.04 M) was added titanium tetraisopropoxide (2 equiv) at 0 °C and the resulting solution was stirred overnight under nitrogen atmosphere at room temperature. The following day titanium tetrachloride (1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 2 equiv) was added and the reaction mixture was stirred for 2.5 hours.  $\text{NaCNBH}_4$  was added (2 equiv) and stirring was kept for 2 more hours. The reaction can be monitored by electrospray MS. The reaction mixture was quenched with saturated solution of  $\text{NaHCO}_3$ , and diluted with EtOAc. The reaction mixture was filtered off and the filtrate was evaporated to yield a residue which was purified by SCX. Quantitative yield.

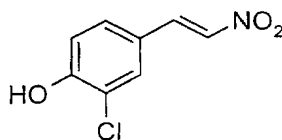
$^1\text{H}$  NMR (MeOH- $d_4$ )  $\delta$ : 8.61 (d, 1H,  $J = 2.4$  Hz), 8.23 (dd, 1H,  $J = 8.7, 2.4$  Hz), 7.40-7.30 (m, 2H), 7.20-7.05 (m, 3H), 7.00-6.75 (m, 3H), 3.82 (q, 1H,  $J = 7.5$  Hz), 2.95 (m, 2H), 2.70 (m, 2H), 1.34 (d, 3H,  $J = 7.5$  Hz).

$^{13}\text{C}$  NMR (MeOH- $d_4$ )  $\delta$ : 167.2, 164.7, 151.6, 146.4, 146.3, 140.9, 138.4, 126.9, 125.5, 123.7, 122.1, 120.0, 109.5, 56.2, 36.0, 28.3, 21.4.

MS (Electrospray): 368.2 ( $\text{M}^+ + 1$ ).

### Intermediates for Examples 475-480

#### Intermediate 1

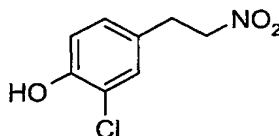


3-Chloro-4-hydroxybenzaldehyde (2 g, 12.8 mmol), nitromethane (4.68 g, 76.6 mmol) and ammonium acetate (3.93 g, 51.1 mmol) are dissolved in 20 mL acetic acid and the reaction mixture is heated at 110 °C. After 3.5 h the reaction mixture is concentrated under reduced pressure and the residue is partitioned between EtOAc and water. Separate the layers and wash the organic layer with brine. Dry with sodium sulfate, filter and



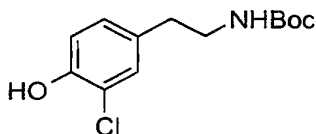
concentrate under reduced pressure. Silica gel chromatography using hexanes: dichloromethane : EtOAc in a 60:35:5 ratio afforded 1.26 g (49 %) of the title compound.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz): 7.90 (d, 1H,  $J = 13.6$  Hz), 7.55 (d, 1H,  $J = 1.8$  Hz), 7.49 (d, 1H,  $J = 13.6$  Hz), 7.41 (d, 1H,  $J = 8.3$  Hz), 7.09 (d, 1H,  $J = 8.3$  Hz), 5.92 (s, 1H),

## Intermediate 2



To a solution of lithium aluminum hydride (.325 g, 8.55 mmol) in 30 mL of THF at 0 °C is added aluminum trichloride (1.14 g, 8.55 mmol). After 5 min the intermediate 1 (.57 g, 2.85 mmol) is added dropwise in 15 mL of THF and the reaction is allowed to stir for 18 h. 100 mL of water and 10 mL of 5 N HCL are added and the reaction mixture is extracted with 3 : 1 n-butanol : toluene. The combined organic layers are washed with brine, dried over sodium sulfate and concentrated. SCX ion-exchange chromatography afforded 335 mg (68%) of the title compound. MS (APCI): ( $M^+ + 1$ ),  $^1\text{H-NMR}$  (DMSO, 400 MHz): 7.14 (m, 1H), 6.92 (m, 1H), 6.83 (m, 1H), 2.86 (d, 1H,  $J = 7.48, 7.05$  Hz), 2.69 (t, 1H,  $J = 7.48, 7.05$  Hz), 2.59 (d, 1H,  $J = 7.48, 7.05$  Hz), 2.50 (d, 1H,  $J = 7.48, 7.05$  Hz).

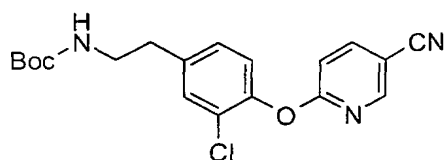
## Intermediate 3



To a solution of the intermediate 2 (400 mg, 2.32 mmol) in 15 mL of THF is added di-tert-butyl dicarbonate (557 mg, 2.56 mmol) and sodium bicarbonate (234 mg, 2.79 mmol). After 18 h the reaction mixture is partitioned between EtOAc and brine. The organic layer is separated and washed with 1 M citric acid and brine. It is dried over sodium sulfate, filtered and concentrated. Silica gel chromatography using 5 – 10 % EtOAc in dichloromethane afforded 430 mg (68 %) of the title compound. MS (APCI): ( $M^+ + 1$ -Boc group),  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz): 7.14 (d, 1H,  $J = 1.5$  Hz), 6.99 (dd, 1H,

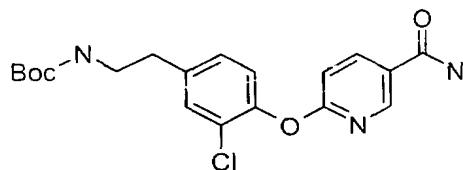
$J = 8.3, 1.9$  Hz), 6.94 (d, 1H,  $J = 7.8$  Hz), 3.32 (m, 2H), 2.70 (t, 2H,  $J = 6.8$  Hz), 1.43 (s, 9H).

#### Intermediate 4



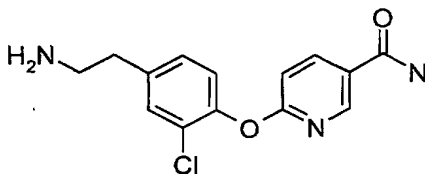
A solution of the intermediate 3 (700 mg, 2.57 mmol), 6-chloronicotinonitrile (392 mg, 2.83 mmol) and sodium hydride (113 mg, 2.83 mmol) is stirred for 18 h. The reaction mixture is partitioned between ethyl acetate and brine. The organic layer is separated, washed with water and brine, dried over sodium sulfate, filtered and concentrated. Silica gel chromatography using 0 – 10 % ethyl acetate in dichloromethane afforded 895 mg (93 %) of the title compound. MS (APCI): ( $M^+ + 1$ -Boc group) 274,  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 400 MHz): 8.42 (d, 1H,  $J = 1.9$  Hz), 7.94 (dd, 1H,  $J = 8.8, 2.4$  Hz), 7.32 (d, 1H,  $J = 1.5$  Hz), 7.08 – 7.25 (m, 3H), 4.61 (bs, 1H), 3.39 (m, 2H), 2.81 (t, 2H,  $J = 6.84$  Hz), 1.43 (s, 9H).

#### Intermediate 5



To a solution of the intermediate 4 (875 mg, 2.34 mmol) in DMSO was added potassium carbonate (161 mg, 1.17 mmol) followed by addition of 30% hydrogen peroxide solution (10 ml) and the reaction was allowed to stir for 18 h. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was washed with water and brine before being dried over sodium sulfate, filtered and concentrated to afford 827 mg (90 %) of the title compound.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 400 MHz): 8.55 (bs, 1H), 8.21 (dd, 1H,  $J = 8.8, 2.4$  Hz), 7.32 (bs, 1H), 7.16 (bs, 2H), 7.04 (d, 1H,  $J = 8.8$  Hz), 4.63 (bs, 1H), 3.39 (m, 2H), 2.81 (t, 2H,  $J = 6.84$  Hz), 1.44 (s, 9H).

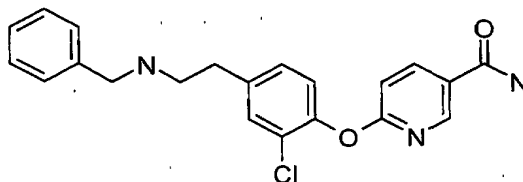
## Intermediate 6



A solution of the intermediate 5 (827 mg, 2.11 mmol) in 25 % TFA in methylene chloride was stirred for 18 h. The reaction mixture was concentrated under reduced pressure, and purified using SCX ion-exchange chromatography to afford 587 mg (95 %) of the title compound. MS (APCI): ( $M^+ + 1$ ) 292.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$  with MeOH (*d*-4), 400 MHz): 8.49 (d, 1H,  $J = 2.4\text{Hz}$ ), 8.21 (dd, 1H,  $J = 8.3, 2.4\text{ Hz}$ ), 7.27 (d, 1H,  $J = 1.5\text{Hz}$ ), 7.11 (m, 2H), 6.96 (d, 1H,  $J = 8.8\text{ Hz}$ ), 2.92 (t, 2H,  $J = 6.9\text{Hz}$ ), 2.72 (t, 2H,  $J = 6.8\text{Hz}$ ).

## Example 475

## 6-[4-(2-Benzylamino-ethyl)-2-chloro-phenoxy]-nicotinamide



The intermediate 6 (100 mg, .342 mmol) and benzaldehyde (435 mg, .411 mmol) were dissolved in 5 mL of methanol while stirring for 18 h.  $\text{NaBH}_4$  (29.4 mg, .68 mmol) was added and the reaction continued for an additional 4 h. The  $\text{NaBH}_4$  was neutralized with a few drops of acetic acid and the reaction mixture was loaded directly onto a 2 g SCX column for purification to afford 103 mg (79 %) of the title compound. MS (APCI): ( $M^+ + 1$ ,  $M^+ + 3$ ) 382, 384.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz): 8.53 (d, 1H,  $J = 2.44\text{Hz}$ ), 8.19 (dd, 1H,  $J = 8.3, 2.4\text{ Hz}$ ), 7.29 – 7.33 (m, 6H), 7.14 – 7.16 (m, 2H), 7.03 (d, 1H,  $J = 8.3\text{ Hz}$ ), 3.83 (s, 2H), 2.92 (m, 2H), 2.83 (m, 2H). \*\* HPLC Purity: 94%, \*\* HPLC Retention time: 1.745 minutes.

By the method outlined for the synthesis of Example 475, the following compounds were prepared.

Example	Name	Mass	NMR / MS / LC/MS
476	6-{2-Chloro-4-[2-(2-methyl-benzylamino)-ethyl]-phenoxy}-nicotinamide	395	<p>(APCI): (<math>M^+ + 1</math>, <math>M^+ + 3</math>) 396, 398</p> <p><math>^1\text{H-NMR}</math> (<math>\text{CDCl}_3</math>, 400 MHz): 8.53 (d, 1H, <math>J = 2.44\text{Hz}</math>), 8.19 (dd, 1H, <math>J = 8.3, 2.4\text{ Hz}</math>), 7.34 (d, 1H, <math>J = 1.95\text{Hz}</math>), 7.26 (m, 1H), 7.12 – 7.18 (m, 5H), 7.03 (d, 1H, <math>J = 7.8\text{Hz}</math>), 3.80 (s, 2H), 2.97 (t, 2H, <math>J = 6.84\text{Hz}</math>), 2.84 (t, 2H, <math>J = 6.84\text{Hz}</math>), 2.32 (s, 3H).</p> <p>**HPLC Purity: 94.6%</p> <p>**HPLC Retention time: 1.842 min.</p>
477	6-{2-Chloro-4-[2-(2-trifluoromethyl-benzylamino)-ethyl]-phenoxy}-nicotinamide	449	<p>(APCI): (<math>M^+ + 1</math>) 450</p> <p>**HPLC Purity: 80.8%</p> <p>**HPLC Retention time: 2.197 min.</p>
478	6-{2-Chloro-4-[2-(3-fluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide	399	<p>(APCI): (<math>M^+ + 1</math>, <math>M^+ + 3</math>) 400, 402</p> <p><math>^1\text{H-NMR}</math> (<math>\text{CDCl}_3</math> with <math>\text{D}_4</math> MeOH, 400 MHz): 8.49 (d, 1H, <math>J = 2.44\text{Hz}</math>), 8.17 (dd, 1H, <math>J = 8.3, 2.4\text{ Hz}</math>), 6.90 – 7.25 (m, 8H), 3.75 (s, 2H), 2.76 –</p>

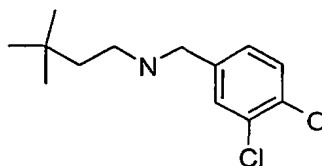
			2.84 (m, 4H).  **HPLC Purity: 93.8%  **HPLC Retention time: 1.799 min.
479	6-{2-Chloro-4-[2-(3-chloro-benzylamino)-ethyl]-phenoxy}-nicotinamide	416	(APCI): ( $M^+$ , $M^++2$ ) 416, 418  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ with $\text{D}_4$ MeOH, 400 MHz): 8.46 (d, 1H, $J=1.95\text{Hz}$ ), 8.12 (dd, 1H, $J=8.8, 2.4\text{Hz}$ ), 7.04 – 7.22 (m, 7H), 6.88 (d, 1H, $J=8.3\text{Hz}$ ), 3.68 (s, 2H), 2.73 – 2.78 (m, 4H).  **HPLC Purity: 93.4%  **HPLC Retention time: 1.857 min.
480	6-{2-Chloro-4-[2-(3-trifluoromethyl-benzylamino)-ethyl]-phenoxy}-nicotinamide	449	(APCI): ( $M^++1$ ) 450•  **HPLC Purity: 81.9%  **HPLC Retention time: 2.275 min.

\*\* HPLC conditions: (10/90 to 90/10 ACN/(0.1%TFA in water) Water's Xterra MS C18 Column 4.6 mm x 50 mm x 5 micron.

### Intermediates for Examples 481-482

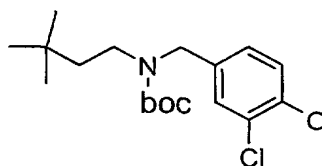
#### Intermediate 1

322



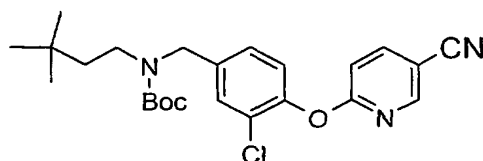
3-Chloro-4-hydroxybenzaldehyde (100 mg, 0.64 mmol) and 3,3-dimethyl-1-butylamine (56 mg, 0.55 mmol) were dissolved in 2 mL methanol containing 3 Å molecular sieves. After 18 hours, sodium borohydride (41 mg, 1.28 mmol) was added and the reaction was continued for another 4 h. The reaction was quenched by the addition of a few drops of acetic acid and purified by SCX ion-exchange chromatography to afford 50 mg (37.6%) of the title compound. MS (APCI): ( $M^+ + 1$ ) 242,  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz): 7.29 (d, 1H,  $J = 1.95$  Hz), 7.10 (dd, 1H,  $J = 8.3, 1.95$  Hz), 6.87 (d, 1H,  $J = 8.3$  Hz), 3.72 (s, 2H), 2.67 (t, 2H,  $J = 8.3$  Hz), 1.48 (t, 2H,  $J = 8.8$  Hz), 0.89 (s, 9H).

## Intermediate 2



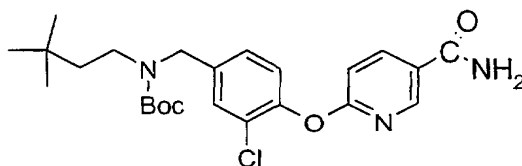
To a solution of the intermediate 1 (50 mg, 0.2 mmol) in 2 mL of THF was added di-tert-butyl dicarbonate (56.5 mg, 0.26 mmol) and sodium bicarbonate (26 mg, 0.31 mmol). After 18 h the reaction mixture was partitioned between EtOAc and brine. The organic layer is separated and washed with 1 M citric acid and brine, after which it was dried over sodium sulfate, filtered and concentrated. Silica gel chromatography using 0 - 5 % EtOAc in dichloromethane afforded 34 mg (48%) of the title compound.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz): 7.21 (s, 1H), 7.04 (m, 1H), 6.96 (d, 1H,  $J = 8.3$  Hz), 5.52 (s, 1H), 4.31 (bs, 2H), 3.14 (m, 2H), 1.56 (m, 11H), 0.85 (s, 9H).

## Intermediate 3



A solution of the intermediate 2 (110 mg, 0.32 mmol), 6-chloronicotinonitrile (49 mg, 0.35 mmol) and sodium hydride (14.2 mg, 0.35 mmol) was stirred for 18 h. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was separated, washed with water and brine, dried over sodium sulfate, filtered and concentrated. Silica gel chromatography using 0 – 5 % ethyl acetate in 60 : 40 hexanes: dichloromethane afforded 23 mg (16 %) of the title compound. MS (APCI): ( $M^+$ +1-Boc group) 344,  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz): 8.42 (dd, 1H,  $J = 2.2, 0.88$  Hz), 7.95 (dd, 1H,  $J = 8.37, 2.2$  Hz), 7.36 (s, 1H), 7.15 – 7.20 (m, 2H), 7.09 (d, 1H,  $J = 8.8$  Hz), 4.40 (bs, 2H), 3.19 (m, 2H), 1.48 (bs, 11H), 0.89 (s, 9H).

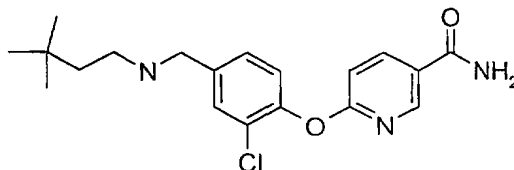
#### Intermediate 4



To a solution of the intermediate 3 (244 mg, 0.55 mmol) in 5 mL of DMSO was added potassium carbonate (38 mg, 0.275 mmol) followed by 30% hydrogen peroxide solution (2 mL) and the reaction was allowed to stir for 18 h. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was washed with water and brine before being dried over sodium sulfate, filtered and concentrated to afford 218 mg (86 %) of the title compound. MS (APCI): ( $M^+$ +1-Boc group) 362.

#### Example 481

6-{2-Chloro-4-[(3,3-dimethylbutylamino)-methyl]-phenoxy}-nicotinamide



A solution of the intermediate 4 (218 mg, 0.47 mmol) in 2.5 mL of 20 % TFA in methylene chloride was stirred for 18 h. After the reaction mixture was concentrated under reduced pressure, SCX ion-exchange chromatography followed by silica gel

chromatography using 5 – 10 % 2 N NH<sub>3</sub> methanol in dichloromethane afforded 151 mg (88 %) of the title compound. MS (APCI): (M<sup>+</sup>+1) 362, <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): 8.53 (d, 1H, J = 2.64 Hz), 7.95 (dd, 1H, J = 8.8, 2.64 Hz), 7.48 (d, 1H, J = 2.2 Hz), 7.29 (dd, 1H, J = 8.36, 2.2 Hz), 7.16 (d, 1H, J = 7.92 Hz), 7.02 (d, 1H, J = 9.24 Hz), 5.93 (vbs, 2H), 3.80 (s, 2H), 2.67 (m, 2H), 1.45 (m, 2H), 0.91 (s, 9H). Purity: 94.2%, Retention time: 1.802 minutes.

The following compound is also prepared by the method outlined for the synthesis of the compound of Example 481.

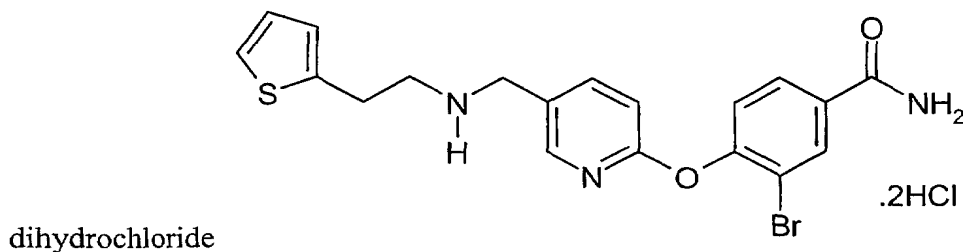
Example	Name	Mass	NMR / LC/MS
482	6-{2-Chloro-4-[(2-thiophen-2-yl-ethylamino)-methyl]-phenoxy}-nicotinamide	387	MS (APCI): (M <sup>+</sup> +1) 388, <sup>1</sup> H-NMR (CDCl <sub>3</sub> , 400 MHz): 8.51 (bs, 1H), 8.19 (dd, 1H, J = 8.3, 1.95 Hz), 7.43 (bs, 1 Hz), 6.81 – 7.24 7.29 (m, 6H), 3.79 (s, 2H), 3.03 (m, 2H), 2.91 (m, 2H).  Purity: 87.1%  Retention time: 1.696 minutes.



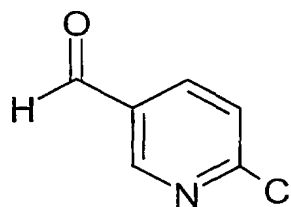
325

**Example 483**

3-Bromo-4-{5-[(2-thiophen-2-yl-ethylamino)-methyl]-pyridin-2-yloxy}-benzamide



Step 1

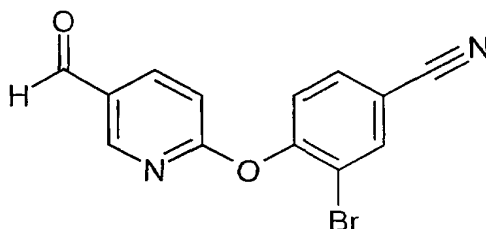


6-Chloro-pyridine-3-carbaldehyde

Combine 6-chloro-nicotino-nitrile ((1.00 g, 7.21 mmol) and toluene (24 mL). Cool the resulting solution at 0 °C and add DIBAL-H (1.0 M in toluene, 7.58 mL, 7.58 mmol) dropwise. Stir the resulting red solution at 0 °C for 1 h. Then, add methanol (2 mL) followed by H<sub>2</sub>SO<sub>4</sub> (aq. 2.0 M, 6 mL). Stir for 1 h at rt. Add CHCl<sub>3</sub>:isopropanol (3/1, 15 mL) and wash with Rochelle's salt solution (20 mL), followed by NaHCO<sub>3</sub> (20 mL) and brine. Dry the combined organic layers over magnesium sulfate, filter and concentrate. Purify by flash chromatography (EtOAc/hexanes 10%) to give the title compound (530 mg, 62%).

Step 2

3-Bromo-4-(5-formyl-pyridin-2-yloxy)-benzonitrile

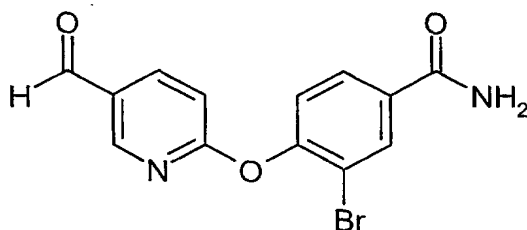


Combine 6-chloro-pyridine-3-carbaldehyde (1.00 g, 7.09 mmol), 3-bromo-4-hydroxy-benzonitrile (1.48 g, 7.80 mmol) in dimethylacetamide (40 mL). Add potassium carbonate (1.47 g, 10.64 mmol) and stir and heat the reaction at 130 °C for 2 h. Let cool

down the reaction to room temperature and poured into water. Filter the precipitate formed, washing with water, to give the title compound (1.55 g, 72%)

### Step 3

#### 3-Bromo-4-(5-formyl-pyridin-2-yloxy)-benzamide



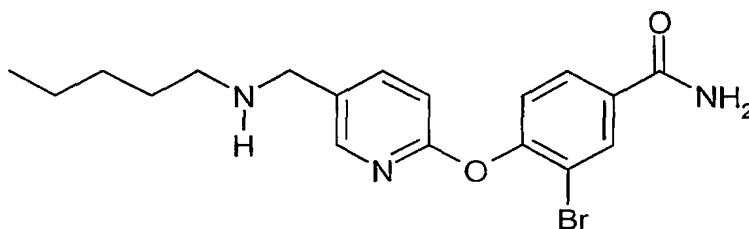
Combine 3-bromo-4-(5-formyl-pyridin-2-yloxy)-benzonitrile (1.60 g, 5.28 mmol) and potassium carbonate (365 mg, 2.64 mmol) in DMSO (40 mL). Cool the reaction mixture at 0 °C. Add hydrogen peroxide (1.59 mL, 5.28 mmol) dropwise and let the reaction stir at room temperature for 2 h. Pour into water and triturate to a white solid with stirring. Filter the white solid and dry to give (852 mg, 82%) of the title compound.

### Step 4

Using a method similar to example 462, using 2-thiophen-2-ylethylamine and 3-bromo-4-(5-formyl-pyridin-2-yloxy)benzamide (step 3) gives the title compound (220 mg, 92%).  
Mass spectrum (ion spray):  $m/z = 433.9$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.11 (d,  $J = 2.2$  Hz, 1H), 8.05 (d,  $J = 2.2$  Hz, 1H), 7.76 (td,  $J = 8.4$  Hz, 2H), 7.22 (d,  $J = 8.4$  Hz, 1H), 7.14 (d,  $J = 5.1$  Hz, 1H), 7.00 (d,  $J = 8.4$  Hz, 1H), 6.93 (dd,  $J = 3.2$  Hz, 5.1 Hz, 1H), 6.83 (d,  $J = 3.2$  Hz, 1H), 6.14 (bs, 1H), 5.87 (bs, 1H), 3.77 (s, 2H), 3.04 (t,  $J = 6.7$  Hz, 2H), 2.93 (t,  $J = 6.7$  Hz, 2H).

### Example 484

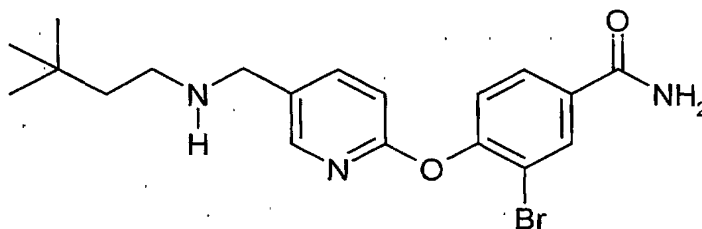
#### 3-Bromo-4-(5-pentylaminomethyl-pyridin-2-yloxy)-benzamide



Using a method similar to example 462, using pentylamine and the benzamide in Example 483, step 3, gives the title compound (158 mg, 65%). Mass spectrum (ion spray):  $m/z = 394.0$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.09 (d,  $J = 2.2$  Hz, 1H), 8.04 (d,  $J = 2.1$  Hz, 1H), 7.75 (d,  $J = 8.6$  Hz, 2H), 7.17 (d,  $J = 8.6$  Hz, 1H), 6.98 (d,  $J = 8.3$  Hz, 1H), 6.59 (bs, 1H), 6.34 (bs, 1H), 3.73 (s, 2H), 2.59 (t,  $J = 6.8$  Hz, 2H), 1.52-1.44 (m, 3H), 1.31-1.25 (m, 4H), 0.86 (t,  $J = 6.8$  Hz, 3H).

#### Example 485

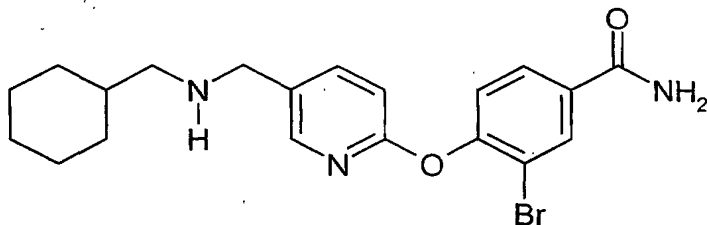
3-Bromo-4-{5-[(3,3-dimethyl-butylamino)-methyl]-pyridin-2-yloxy}-benzamide



Using a method similar to example 462, using cyclohexylmethylamine and the benzamide in Example 483, step 3, gives the title compound (168 mg, 66%). Mass spectrum (ion spray):  $m/z = 408.0$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 8.19 (s, 1H), 8.07 (bs, 1H), 8.00 (s, 1H), 7.90 (d,  $J = 8.6$  Hz, 1H), 7.83 (d,  $J = 8.5$  Hz, 1H), 7.48 (bs, 1H), 7.28 (d,  $J = 8.5$  Hz, 1H), 7.08 (d,  $J = 8.5$  Hz, 1H), 3.63 (s, 2H), 2.46 (t,  $J = 7.8$  Hz, 2H), 2.04 (bs, 1H), 1.33 (t,  $J = 7.8$  Hz, 2H), 0.84 (s, 9H).

#### Example 486

3-Bromo-4-{5-[(cyclohexylmethyl-amino)-methyl]-pyridin-2-yloxy}-benzamide

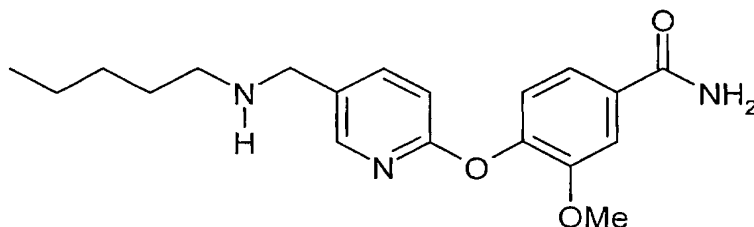


Using a method similar to example 462, using cyclohexylmethylamine and the benzamide in Example 483 step3, affords the title compound (209 mg, 80%). Mass spectrum (ion spray):  $m/z = 418.2$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 8.18 (s, 1H), 8.07 (bs, 1H), 7.99 (s, 1H), 7.89 (d,  $J = 8.4$  Hz, 1H), 7.83 (d,  $J = 8.4$  Hz, 1H), 7.48 (bs, 1H), 7.28 (d,  $J = 8.4$  Hz,

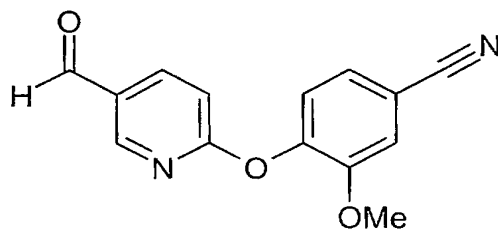
1H), 7.08 (d, J = 8.4 Hz, 1H), 3.62 (s, 2H), 2.28 (d, J = 6.5 Hz, 2H), 1.76-1.57 (m, 5H), 1.40-1.30 (m, 1H), 1.22-1.06 (m, 3H), 0.88-0.77 (m, 2H).

**Example 487**

3-Methoxy-4-(5-pentylaminomethyl-pyridin-2-yloxy)-benzamide

**Step 1**

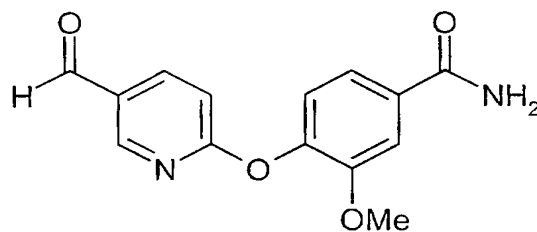
4-(5-Formyl-pyridin-2-yloxy)-3-methoxy-benzonitrile



Using a method similar to example 483 (step 2), using 4-hydroxy-3-methoxy-benzonitrile (1.18 g, 7.91 mmol) gives the title compound (1.71 g, 94%).

**Step 2**

4-(5-Formyl-pyridin-2-yloxy)-3-methoxy-benzamide



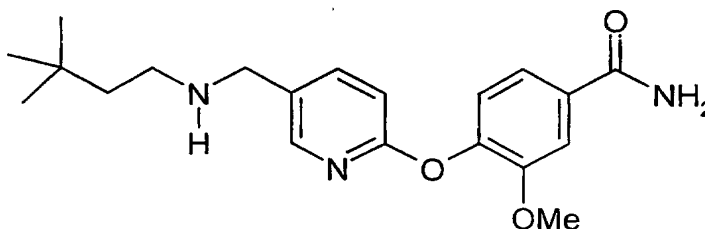
Using a method similar to example 483 (step 3), using 4-(5-formyl-pyridin-2-yloxy)-3-methoxy-benzonitrile (1.71 g, 6.74 mmol) gives the title compound (1.107 g, 60%).

**Step 3**

Using a method similar to example 462, using pentylamine and the benzamide in step 2, gives the title compound (174 mg, 69%). Mass spectrum (ion spray):  $m/z = 344.3$  (M+1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.02 (d,  $J = 1.9$  Hz, 1H), 7.69 (dd,  $J = 2.1$  Hz, 8.6 Hz, 1H), 7.53 (d,  $J = 1.7$  Hz, 1H), 7.32 (dd,  $J = 1.7$  Hz, 8.1 Hz, 1H), 7.10 (d,  $J = 8.1$  Hz, 1H), 6.92 (d,  $J = 8.6$  Hz, 1H), 6.51 (bs, 1H), 6.25 (bs, 1H), 3.76 (s, 3H), 3.71 (s, 2H), 2.58 (t,  $J = 7.6$  Hz, 2H), 1.51-1.43 (m, 3H), 1.31-1.24 (m, 4H), 0.86 (t,  $J = 6.6$  Hz, 3H).

### Example 488

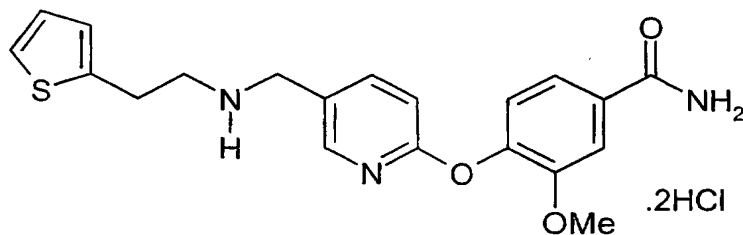
4-{5-[(3,3-Dimethyl-butylamino)-methyl]-pyridin-2-yloxy}-3-methoxy-benzamide



Using a method similar to example 462, using 3,3-dimethylbutylamine and the benzamide in Example 487, step 2, gives the title compound (170 mg, 65%). Mass spectrum (ion spray):  $m/z = 358.3$  (M+1);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 7.98 (bs, 1H), 7.95 (s, 1H), 7.75 (d,  $J = 8.2$  Hz, 1H), 7.59 (s, 1H), 7.49 (d,  $J = 8.5$  Hz, 1H), 7.36 (bs, 1H), 7.14 (d,  $J = 8.5$  Hz, 1H), 6.94 (d,  $J = 8.5$  Hz, 1H), 3.71 (s, 3H), 3.61 (s, 2H), 2.45 (t,  $J = 8.4$  Hz, 2H), 1.32 (t,  $J = 8.4$  Hz, 2H), 0.84 (s, 9H).

### Example 489

3-Methoxy-4-{5-[(2-thiophen-2-yl-ethylamino)-methyl]-pyridin-2-yloxy}-benzamide



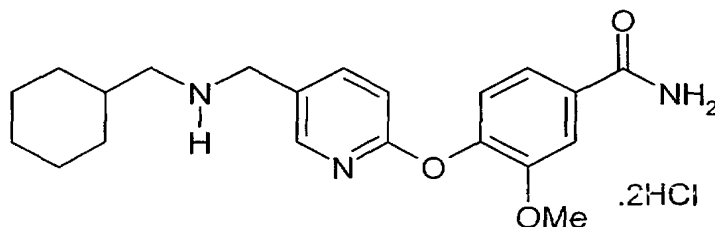
dihydrochloride

Using a method similar to example 462, using 2-thiophen-2-ylethylamine and the benzamide in Example 489, step 2, gives the title compound (188 mg, 67%). Mass spectrum (ion spray):  $m/z = 384.2$  (M+1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.01 (s, 1H), 7.67 (d,  $J = 8.3$  Hz, 1H), 7.54 (s, 1H), 7.34 (d,  $J = 7.9$  Hz, 1H), 7.13-7.08 (m, 2H), 6.94-6.86 (m, 2H),

6.81 (s, 1H), 6.67 (bs, 1H), 6.42 (bs, 1H), 3.79-3.71 (m, 5H), 3.05-2.98 (m, 2H), 2.93-2.86 (m, 2H).

#### Example 490

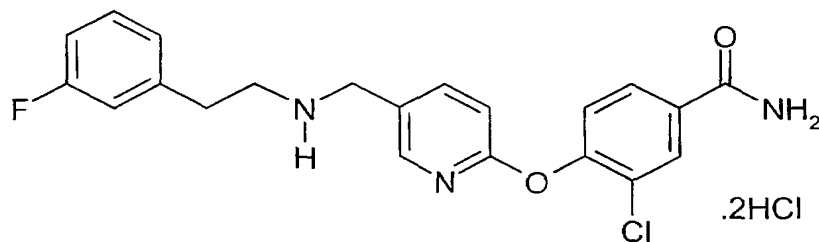
4-{5-[(Cyclohexylmethyl-amino)-methyl]-pyridin-2-yloxy}-3-methoxy-benzamide dihydrochloride



Using a method similar to example 462, using cyclohexylmethylamine and the benzamide in Example 487, step 2, gives the title compound (179 mg, 66%). Mass spectrum (ion spray):  $m/z = 370.3$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.01 (d,  $J = 2.0$  Hz, 1H), 7.69 (dd,  $J = 2.2$  Hz, 8.2 Hz, 1H), 7.53 (d,  $J = 1.8$  Hz, 1H), 7.32 (dd,  $J = 1.8$  Hz, 8.2 Hz, 1H), 7.09 (d,  $J = 8.0$  Hz, 1H), 6.91 (d,  $J = 8.4$  Hz, 1H), 6.52 (bs, 1H), 6.27 (bs, 1H), 3.76 (s, 3H), 3.69 (s, 2H), 2.41 (d,  $J = 6.6$  Hz, 2H), 1.74-1.60 (m, 5H), 1.46-1.36 (m, 2H), 1.26-1.09 (m, 3H), 0.92-0.81 (m, 2H).

#### Example 491

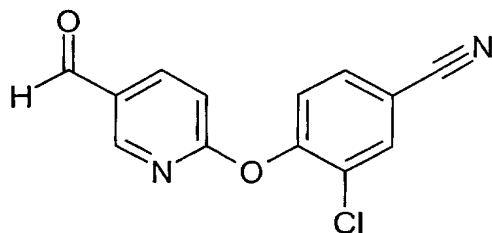
3-Chloro-4-(5-{[2-(3-fluoro-phenyl)-ethylamino]-methyl}-pyridin-2-yloxy)-benzamide dihydrochloride



Step 1

3-Chloro-4-(5-formyl-pyridin-2-yloxy)-benzonitrile

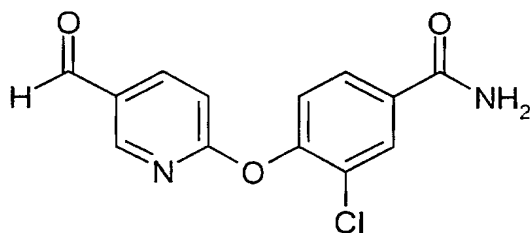
331



Using a method similar to example 483 (step 2), using 3-chloro-4-hydroxy-benzonitrile (527 mg, 3.43 mmol) gives the title compound (573 mg, 76%).

### Step 2

3-Chloro-4-(5-formylpyridin-2-yloxy)-benzamide



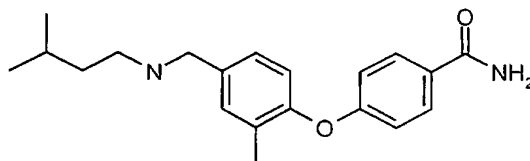
Using a method similar to example 483 (step 3) using 3-chloro-4-(5-formylpyridin-2-yloxy)-benzonitrile (573 mg, 2.36 mmol) gives the title compound (404 mg, 62%).

### Step 3

Using a method similar to example 462, using fluorophenethylamine and the benzamide in step 2, gives the title compound (84 mg, 97%). Mass spectrum (ion spray):  $m/z$  = 400.2 ( $M+1$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 8.01 (s, 1H), 7.93 (d,  $J$  = 2.0 Hz, 1H), 7.73-7.68 (m, 2H), 7.24-7.19 (m, 2H), 6.99-6.86 (m, 4H), 6.51 (bs, 1H), 6.33 (bs, 1H), 3.74 (s, 2H), 2.87 (t,  $J$  = 6.6 Hz, 2H), 2.79 (t,  $J$  = 6.6 Hz, 2H).

### Example 492

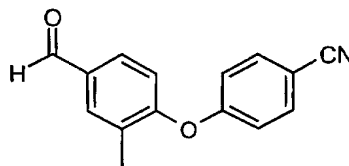
4-{2-Methyl-4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide



332

## Step 1

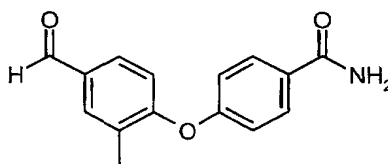
## 4-(4-Formyl-2-methyl-phenoxy)-benzonitrile



Dissolve 3-hydroxy-3-methyl-benzaldehyde (1.02g, 7.49 mmol) in DMF (10mL), add  $K_2CO_3$  (1.45g, 10.49 mmol) and 4-fluorobenzonitrile (906 mg, 7.49 mmol), heat the mixture at 130°C overnight. Add water and extract the aqueous layer with EtOAc. Combine organic layers and dry over  $Na_2SO_4$ . Eliminate the solvent and purify by flash chromatography on silica gel (eluent: EtOAc/hexane 15/85) to give the title compound (920 mg, 52%). TLC:  $R_f$  in EtOAc/hexane 20/80: 0.32.  $^1H$ -NMR ( $CDCl_3$ , 200 MHz): 9.96 (s, 1H), 7.84-7.61 (m, 4H), 7.05-6.98 (m, 3H), 2.31 (s, 3H).

## Step 2

## 4-(4-Formyl-2-methyl-phenoxy)-benzamide



The compound of step 1 is subject to hydrolysis using hydrogen peroxide and potassium carbonate. The details of the hydrolysis procedure to form the amide from nitrile have been described exhaustively elsewhere in this document.

$^1H$ -NMR ( $CDCl_3$ , 200 MHz): 9.94 (s, 1H), 7.87-7.65 (m, 4H), 7.04-6.95 (m, 3H), 5.92 (bs, 2H), 2.34 (s, 3H).

## Step3

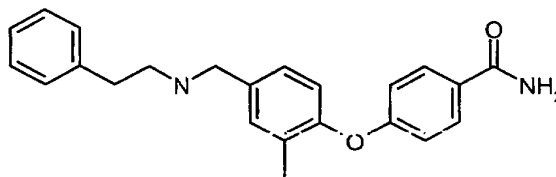
Combine 3-methyl-butylamine (93 $\mu$ l, 0.8 mmol), the aldehyde from Example 492, step 2 above and 3A molecular sieves (1.8 g) in methanol (5 mL), stir the mixture at room temperature overnight. Add  $NaBH_4$  (149 mg, 4.0 mmol) and stir at room temperature for 3 hours. Filtrate the mixture over celite and eliminate the solvent. Purify crude mixture by



SCX column to obtain the title compound (190 mg, 73%). Electrospray MS M+1 ion = 327. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): 7.87-7.80 (m, 2H), 7.32-7.20 (m, 2H), 6.96-6.85 (m, 3H), 3.76 (s, 2H), 2.68-2.60 (m, 2H), 2.16 (s, 3H), 1.69-1.39 (m, 3H), 0.91 (d, 6H, J= 7.0 Hz).

#### Example 493

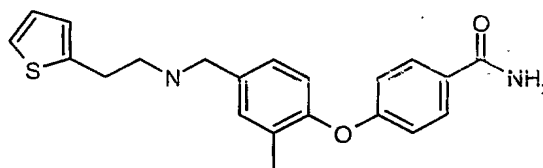
4-[2-Methyl-4-(phenethylamino-methyl)-phenoxy]-benzamide



Compound 2 was prepared from aldehyde described in Example 492, step 2 and phenethylamine using the reductive amination conditions described above. Electrospray MS M+1 ion = 361. <sup>1</sup>H -NMR (CDCl<sub>3</sub>, 200 MHz): 7.87-7.80 (m, 2H), 7.31-7.15 (m, 7H), 6.93-6.83 (m, 3H), 3.76 (s, 2H), 2.84 (s, 4H), 2.14 (s, 3H).

#### Example 494

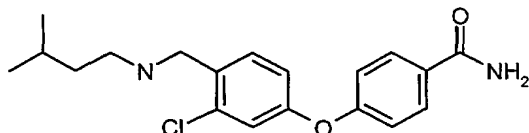
4-{2-Methyl-4-[(2-thiophen-2-yl-ethylamino)-methyl]-phenoxy}-benzamide



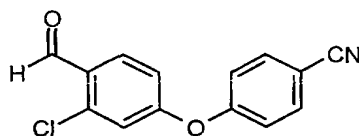
Compound 3 was prepared from aldehyde described in Example 492, step 2 and 2-thiophen-2-yl-ethylamine using the reductive amination conditions described above. Electrospray MS M+1 ion = 367. <sup>1</sup>H -NMR (CDCl<sub>3</sub>, 200 MHz): 7.85-7.81 (m, 2H), 7.26-7.17 (m, 3H), 6.95-6.85 (m, 5H), 3.76 (s, 2H), 3.10-3.02 (m, 2H), 2.91-2.84 (m, 2H), 2.15 (s, 3H).

**Example 495**

4-{3-Chloro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide

**Step 1**

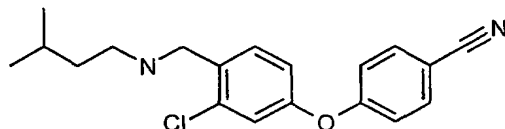
4-(3-Chloro-4-formyl-phenoxy)-benzonitrile



Dissolve 2-chloro-4-hydroxy-benzaldehyde (1.09g, 7.01 mmol) in DMF (10mL), add  $K_2CO_3$  (1.06g, 7.7 mmol) and 4-fluorobenzonitrile (932 mg, 7.7 mmol), heat the mixture at 130°C overnight. Add water and extract the aqueous layer with EtOAc. Combine organic layers and dry over  $Na_2SO_4$ . Eliminate the solvent and purify by flash chromatography on silica gel (eluent: EtOAc/hexane 15/85) to give the title compound (240 mg, 14%).  $^1H$ -NMR ( $CDCl_3$ , 300 MHz): 10.40 (s, 1H), 7.98 (d, 1H,  $J$  = 8.6 Hz), 7.74-7.71 (m, 2H), 7.17-7.00 (m, 4H).

**Step 2**

4-{3-Chloro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzonitrile



The reductive amination was done in the conditions described in Example 492, step 3 using the aldehyde described above. The crude mixture was purified by flash chromatography (EtOAc/hexane 20/80) to obtain the title compound (105 mg, 68%). Electrospray MS  $M+1$  ion = 329.  $^1H$ -NMR ( $CDCl_3$ , 200 MHz): 7.64-7.59 (m, 2H), 7.45 (d, 1H,  $J$  = 8.3 Hz), 7.09-6.92 (m, 4H), 3.8 (s, 2H), 2.67 (t, 2H,  $J$  = 7.5 Hz), 1.75-1.56 (m, 1H), 1.43 (q, 1H,  $J$  = 7.5 Hz), 0.90 (d, 6H,  $J$  = 6.8 Hz).

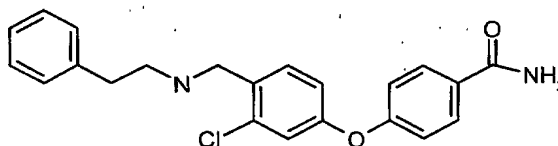
## Step 3

The compound of step 2 above is subject to hydrolysis using hydrogen peroxide and potassium carbonate. The details of the hydrolysis procedure to form the amide form nitrile have been described exhaustively elsewhere in this document.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz): 7.92-7.89 (m, 2H), 7.47 (d, 1H,  $J = 8.3$  Hz), 7.11-6.98 (m, 4H), 3.86 (s, 2H), 2.64 (t, 2H,  $J = 7.7$  Hz), 1.66-1.55 (m, 1H), 1.44 (q, 2H,  $J = 7.7$  Hz), 0.91 (d, 6H,  $J = 6.6$  Hz).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 300 MHz): 167.6, 157.4, 153.5, 131.9, 129.9, 129.0, 127.0, 126.3, 117.5, 115.3, 115.1, 47.1, 35.5, 23.5, 19.1.

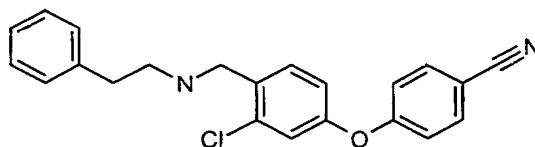
## Example 496

4-[3-Chloro-4-(phenethylamino-methyl)-phenoxy]-benzamide



## Step 1

4-[3-Chloro-4-(phenethylamino-methyl)-phenoxy]-benzonitrile



The reductive amination was done in the conditions described in Example 492, step 3 using the aldehyde described for compound 4 (step 1). The crude mixture was purified by flash chromatography (EtOAc/hexane 20/80) to obtain the title compound (101 mg, 59%). Electrospray MS  $M+1$  ion = 363.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz): 7.64-7.59 (m, 2H), 7.42-7.20 (m, 6H), 7.07-6.89 (m, 4H), 3.89 (s, 2H), 2.99-2.81 (m, 4H).

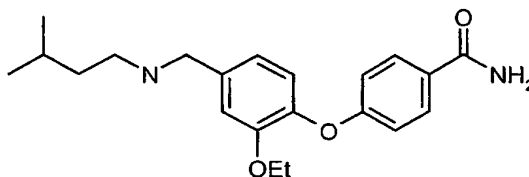
## Step 2

The compound of step 1 above is subject to hydrolysis using hydrogen peroxide and potassium carbonate. The details of the hydrolysis procedure to form the amide form nitrile have been described exhaustively elsewhere in this document.

Electrospray MS M+1 ion = 381.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 200 MHz): 7.92-7.85 (m, 2H), 7.39 (d, 1H,  $J = 8.3$  Hz), 7.30-7.12 (m, 5H), 7.06-6.91 (m, 4H), 3.84 (s, 2H), 2.83 (s, 4H).

#### Example 497

4-{2-Ethoxy-4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide (47J-3179-381, LSN 2120309)



Dissolve 3-ethoxy-4-hydroxy-benzaldehyde (2.57 g, 15.45 mmol) in DMF (20mL), add  $\text{K}_2\text{CO}_3$  (2.33 g, 16.86 mmol) and 4-fluorobenzonitrile (1.70 g, 14.05 mmol), heat the mixture at  $130^\circ\text{C}$  overnight. Add water and extract the aqueous layer with EtOAc.

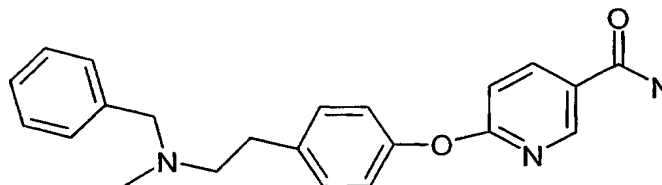
Combine organic layers and dry over  $\text{Na}_2\text{SO}_4$ . Eliminate the solvent and purify by flash chromatography on silica gel (eluent: EtOAc/hexane 15/85) to get a mixture of two compounds (1.45 g). This mixture (240 mg) is submitted to the reductive amination conditions described for compound 1 (step 3) using 3-methyl-butylamine to obtain a mixture of two compounds which is subject to hydrolysis using hydrogen peroxide and potassium carbonate in the conditions described elsewhere in this document. This mixture is purified by flash chromatography (EtOAc and  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  10%) and then the title compound is isolated after HPLC (Column: XTerraMSC18 (5 $\mu\text{m}$ , 19x100 mm). Isocratic mode: 55/45 Ammonium bicarbonate-pH 9-/Acetonitrile. Flow: 10mL/min).

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 200 MHz): 7.82-7.78 (m, 2H), 7.14-6.83 (m, 5H), 4.01 (q, 2H,  $J = 6.8$  Hz), 3.76 (s, 2H), 2.66-2.58 (m, 2H), 1.70-1.39 (m, 3H), 1.17 (t, 3H,  $J = 7.0$  Hz), 0.91 (d, 6H,  $J = 6.7$  Hz).  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 300 MHz): 172.2, 163.6, 152.8, 144.4, 139.4, 130.8, 128.6, 123.8, 122.8, 116.9, 116.3, 65.9, 54.6, 39.8, 27.9, 23.4, 15.3.

#### Example 498

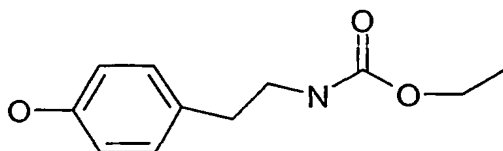
337

## 6-{4-[2-(Benzyl-methyl-amino)-ethyl]-phenoxy}-nicotinamide



## Step 1

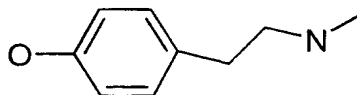
## [2-(4-Hydroxy-phenyl)-ethyl]-carbamic acid ethyl ester



Add dropwise via an addition funnel a solution of ethyl chloroformate (0.74mL, 7.7mmol) in tetrahydrofuran (7mL) to a stirred solution of tyramine (1.0g, 7.3mmol), sodium hydroxide (0.7g, 17.1mmol), and water (7mL). Stir at room temperature for 18 hours then pour the reaction into 1 N aqueous hydrochloric acid so the pH = 1-2. Extract with ethyl acetate (3x25mL). Dry the combined ethyl acetate extracts over sodium chloride/magnesium sulfate, filter, and concentrate on a rotary evaporator to yield 1.3g, 6.2mmol of [2-(4-hydroxy-phenyl)-ethyl]-carbamic acid ethyl ester:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.00 MHz): 7.01 (d, 2H); 6.78 (d, 2H); 6.26 (s, 1H); 4.78 (s, 1H); 4.14-4.09 (m, 2H); 3.40-3.38 (m, 2H); 2.74-2.69 (m, 2H); 1.24-1.19 (m, 3H).

## Step 2

## 4-(2-Methylamino-ethyl)-phenol

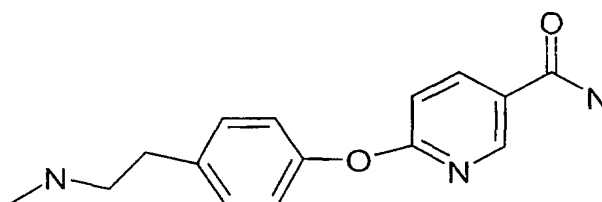


Add dropwise via an addition funnel a solution of [2-(4-Hydroxy-phenyl)-ethyl]-carbamic acid methyl ester (13.0g, 62.2mmol) in tetrahydrofuran (100mL) to a stirred solution at 0 °C of 1.0M lithium aluminum hydride in tetrahydrofuran (156mL) and

tetrahydrofuran (250mL). Reflux for 18 hours, cool to 0 °C, quench with saturated aqueous ammonium chloride then stir at room temperature for 3 hours. Filter off the aluminum salts, concentrate on a rotary evaporator, and dry under vacuum to yield 6.6g of 4-(2-methylamino-ethyl)-phenol: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300.00 MHz): 6.97 (d, 2H); 6.65 (d, 2H); 2.65-2.55 (m, 4H); 2.28 (s, 3H).

## Step 3

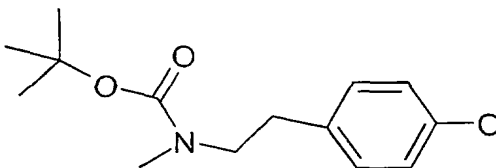
## 6-[4-(2-Methylamino-ethyl)-phenoxy]-nicotinamide



Combine 4-(2-methylamino-ethyl)-phenol (1.0g, 6.6mmol), 6-chloronicotinamide (1.0g, 6.6mmol), and cesium carbonate (4.3g, 13.2mmol) in N,N-dimethylformamide (30mL), stir and heat at 85 °C for 18 hours. Cool to room temperature and evaporate on a rotary evaporator to yield the crude product (1.3g). The crude product is purified by flash column chromatography on silica gel eluting with 1% conc. ammonium hydroxide / 10% ethanol in chloroform then ethanol to yield 6-[4-(2-Methylamino-ethyl)-phenoxy]-nicotinamide (0.4g, 1.5mmol): <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300.00 MHz): 8.58 (d, 1H); 8.22 (dd, 1H); 7.26-7.23 (m, 2H); 7.05-7.02 (m, 3H); 3.32 (br, 2H); 2.69 (m, 5H); 2.29 (m, 4H) m/z = 271.87(M+1); HPLC = 99% (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6mmx15cmx5micron, λ=254nm.

## Step 4

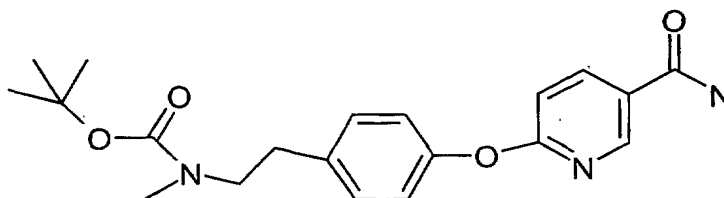
## [2-(4-Hydroxy-phenyl)-ethyl]-methyl-carbamic acid tert-butyl ester



Combine di-tert-butyl dicarbonate (9.7g, 44.5mmol), 4-(2-methylamino-ethyl)-phenol (5.6g, 37.1mmol), and tetrahydrofuran (150mL) and stir at room temperature for 18 hours. Concentrate on a rotary evaporator to yield the crude product. The crude product is purified by flash column chromatography on silica gel eluting with 25% ethyl acetate in hexanes to yield [2-(4-hydroxy-phenyl)-ethyl]-methyl-carbamic acid tert-butyl ester (7.7g, 30.7mmol):  $^1\text{H}$  NMR( $\text{CDCl}_3$ , 300.00 MHz): 7.00 (d, 2H); 6.76 (d, 2H); 6.39 (s, 1H); 3.40 (t, 2H); 2.81 (s, 3H); 2.73 (t, 2H); 1.42 (s, 9H).

### Step 5

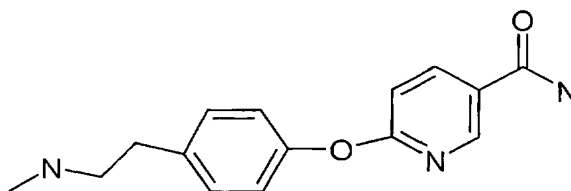
{2-[4-(5-Carbamoyl-pyridin-2-yloxy)-phenyl]-ethyl}-methyl-carbamic acid tert-butyl ester



Combine [2-(4-hydroxy-phenyl)-ethyl]-methyl-carbamic acid tert-butyl ester (5.0g, 19.9mmol), 6-chloronicotinamide (3.1g, 19.9mmol), and cesium carbonate (12.9g, 39.8mmol), in N,N-dimethylformamide (90mL), stir and heat at 85 °C for 18 hours. Cool to room temperature and evaporate on a rotary evaporator to yield the crude product (9.5g). The crude product is purified by flash column chromatography on silica gel eluting with (0.5% conc. ammonium hydroxide / 5% ethanol) to (1% conc. ammonium hydroxide / 10% ethanol) in chloroform to yield {2-[4-(5-carbamoyl-pyridin-2-yloxy)-phenyl]-ethyl}-methyl-carbamic acid tert-butyl ester (6.5g, 17.5mmol):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.00 MHz): 8.60 (s, 1H); 8.18-8.14 (m, 1H); 7.24-7.24 (m, 2H); 7.07 (d, 2H); 6.94 (d, 1H); 5.98 (br, 2H); 3.47-3.42 (m, 2H); 2.85-2.85 (m, 5H); 1.42 (s, 9H).

### Step 6

6-[4-(2-Methylamino-ethyl)-phenoxy]-nicotinamide



Add dropwise via an addition funnel, a solution of trifluoroacetic acid (30mL) in dichloromethane (100mL) to a stirred solution at 0 °C of {2-[4-(5-carbamoyl-pyridin-2-yloxy)-phenyl]-ethyl}-methyl-carbamic acid tert-butyl ester (11.4g, 30.7mmol) in 1,2-dichloromethane (400mL). Warm the mixture to room temperature and stir for 18 hours. Evaporate on a rotary evaporator to yield the crude trifluoroacetic acid salt. Dissolve the salt in methanol (150mL) and 1,2-dichloromethane (150mL) then combine with MP-carbonate resin (50g @ 2.55eq/g) (available from Argonaut Technologies). Stir for 18 hours at room temperature, filter, wash the resin with 1,2-dichloromethane (3 x 75mL), and evaporate the filtrate on a rotary evaporator to yield 6-[4-(2-Methylamino-ethyl)-phenoxy]-nicotinamide (8.1g, 29.9mmol).

#### Step 7

Combine 6-[4-(2-Methylamino-ethyl)-phenoxy]- nicotinamide (135mg, 0.5mmol), benzaldehyde (53μL, 0.52mmol), sodium triacetoxyborohydride (0.21g, 1.0mmol), acetic acid (30 μL, 0.52mmol), tetrahydrofuran (1mL), and 1,2-dichloroethane (5mL) then stir at room temperature for 18 hours. Dilute the reaction with saturated aqueous sodium bicarbonate solution and extract with ethyl acetate (3 x 50mL). Dry the combined ethyl acetate extracts with sodium chloride/magnesium sulfate, filter, and concentrate on a rotary evaporator to yield 200mg of the crude product. The crude product is purified by flash column chromatography on silica gel eluting with (0.5% conc. ammonium hydroxide / 5% ethanol) to (1% conc. ammonium hydroxide / 10% ethanol) in chloroform to yield 6-{4-[2-(benzyl-methyl-amino)-ethyl]-phenoxy}-nicotinamide (106mg, 0.29mmol):  $m/z = 362.07(M+1)$ ;  $^1H$  NMR ( $CDCl_3$ , 300.00 MHz): 8.58 (s, 1H); 8.16 (dd, 3.0 Hz, 1H); 7.33-7.22 (m, 7H); 7.05 (d, 2H); 6.95 (d, 1H); 5.86 (br s, 2H); 3.63 (s, 2H); 2.89-2.72 (m, 4H); 2.34 (s, 3H), HPLC = 100% (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax® SB-Phenyl 4.6mmx15cmx5micron,  $\lambda=254nm$ ).



By the method of Example 498 the following compounds were prepared, isolated as the free base except where noted:

Example	Name	Data		
		Mass spectrum (ion spray): m/z (M+1)	HPLC(5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6mmx15cmx5micron, $\lambda$ =254nm)	
			Purity	Retention Time (minutes)
499	6-{4-[2-(Methyl-thiophen-2-ylmethyl-amino)-ethyl]-phenoxy}-nicotinamide	367.95	99	5.86
500	6-(4-{2-[Methyl-(3-methyl-butyl)-amino]-ethyl}-phenoxy)-nicotinamide	342.07	99	5.91
501	6-{4-[2-(Isobutyl-methyl-amino)-ethyl]-phenoxy}-nicotinamide	327.4	97	5.73
502	6-{4-[2-(Bicyclo[2.2.1]hept-5-en-2-ylmethyl-methyl-amino)-ethyl]-phenoxy}-nicotinamide	378.5	99	6.03
503	6-{4-[2-(Cyclohexylmethyl-methyl-amino)-ethyl]-phenoxy}-nicotinamide	368.5	100	6.04

504	6-(4-{2-[Methyl-(2-phenoxy-benzyl)-amino]-ethyl}-phenoxy)-nicotinamide	454.5	99	6.32
505	6-(4-{2-[Methyl-(2-methyl-benzyl)-amino]-ethyl}-phenoxy)-nicotinamide	376.5	99	5.98
506	6-(4-{2-[(3-Chloro-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	395.9	100	6.02
507	6-(4-{2-[(2-Chloro-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	395.9	100	5.96
508	6-(4-{2-[(4-Fluoro-2-trifluoromethyl-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	448.4	100	6.08
509	6-(4-{2-[(3-Bromo-4-fluoro-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	458.3	100	6.04
510	6-(4-{2-[(2-Chloro-6-fluoro-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	413.9	100	5.93
511	6-{4-[2-(Cyclohexyl-methyl-amino)-ethyl]-phenoxy}-nicotinamide	354.5	100	5.89

512	6-(4-{2-[Methyl-(2-trifluoromethoxy-benzyl)-amino]-ethyl}-phenoxy)-nicotinamide	446.4	99	6.13
513	6-(4-{2-[(3-Fluoro-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	380.4	100	5.90
514	6-(4-{2-[Methyl-(3-phenyl-1H-pyrazol-4-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	428.5	100	5.79
515	6-(4-{2-[(1,5a,6,9,9a,9b-Hexahydro-4H-dibenzofuran-4a-ylmethyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	460.3	76	6.28
516	6-(4-{2-[Methyl-(2,4,6-trimethyl-cyclohex-3-enylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	408.6	76	6.26
517	6-(4-{2-[(5-Chloro-1-methyl-3-trifluoromethyl-1H-pyrazol-4-ylmethyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	467.9	100	5.94
518	6-{4-[2-(Cyclohex-3-enylmethyl-methyl-amino)-ethyl]-phenoxy}-nicotinamide	366.5	86	5.94

519	6-{4-[2-(Dec-4-enyl-methyl-amino)-ethyl]-phenoxy}-nicotinamide	410.6	93	6.45
520	6-(4-{2-[Methyl-(2-phenyl-but-2-enyl)-amino]-ethyl}-phenoxy)-nicotinamide	402.5	100	6.10
521	6-(4-{2-[(3-Furan-2-yl-2-phenyl-allyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	454.5	84	6.23
522	6-(4-{2-[(2-Methoxy-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	392.2	98	5.99
523	6-(4-{2-[(3-Chloro-4-fluoro-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	414.5	99	6.03
524	6-(4-{2-[Methyl-(3-methyl-benzyl)-amino]-ethyl}-phenoxy)-nicotinamide	376.2	100	5.99
525	6-(4-{2-[Methyl-(3-trifluoromethyl-benzyl)-amino]-ethyl}-phenoxy)-nicotinamide	430.18	100	6.07
526	6-(4-{2-[(2,6-Difluoro-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	398.17	100	5.88

527	6-(4-{2-[Methyl-(3-methyl-thiophen-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	382.17	96	5.93
528	6-(4-{2-[Methyl-(3-phenoxy-benzyl)-amino]-ethyl}-phenoxy)-nicotinamide	454.21	99	6.28
529	6-(4-{2-[Methyl-(2-trifluoromethyl-benzyl)-amino]-ethyl}-phenoxy)-nicotinamide	430.15	100	6.03
530	6-{4-[2-(Methyl-thiophen-3-ylmethyl-amino)-ethyl]-phenoxy}-nicotinamide	368.13	100	6.85
531	6-{4-[2-(Cyclopentylmethyl-methyl-amino)-ethyl]-phenoxy}-nicotinamide	354.2	100	5.93
532	6-(4-{2-[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-ylmethyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	414.18	97	5.71
533	6-(4-{2-[(2,5-Bis-trifluoromethyl-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	498.13	100	6.23

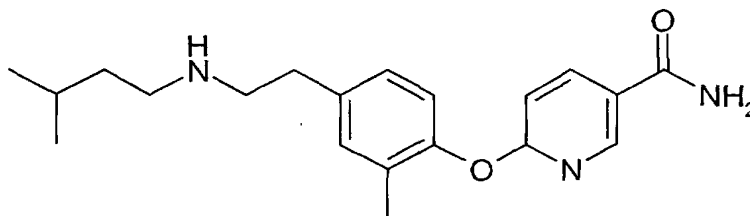
534	6-(4-{2-[(3-Cyclopentyloxy-4-methoxy-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	476.24	100	6.18
535	6-(4-{2-[(2-Fluoro-6-trifluoromethyl-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	448.16	100	6.02
536	6-(4-{2-[Methyl-(4-trifluoromethyl-cyclohexyl)-amino]-ethyl}-phenoxy)-nicotinamide	422.21	100	6.04
537	6-(4-{2-[(4-Chloro-3-trifluoromethyl-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	464.13	100	6.17
538	6-(4-{2-[Methyl-(6-methyl-cyclohex-3-enylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	380.22	90	6.05
539	6-{4-[2-(Cyclohex-1-enylmethyl-methyl-amino)-ethyl]-phenoxy}-nicotinamide	366.2	84	5.98
540	4-({2-[4-(5-Carbamoyl-pyridin-2-yloxy)-phenyl]-ethyl}-methyl-amino)-piperidine-1-carboxylic acid ethyl ester	427.22	100	5.79

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541	6-(4-{2-[(2-Fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	448.16	100	6.11
542	6-(4-{2-[(3,4-Dimethyl-cyclohexyl)-methyl-amino]-ethyl}-phenoxy)-nicotinamide	382.26	99	6.11
543	6-(4-{2-[Methyl-(tetrahydrothiophen-3-yl)-amino]-ethyl}-phenoxy)-nicotinamide	358.16	99	5.74
544	6-{4-[2-(Bicyclo[2.2.1]hept-5-en-2-yl-methyl-amino)-ethyl]-phenoxy}-nicotinamide	364.5	99	5.82

**Example 545**

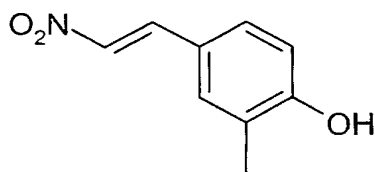
6-{2-Methyl-4-[2-(3-methyl-butylamino)-ethyl]-phenoxy}-nicotinamide



Step 1

2-Methyl-4-(2-nitro-vinyl)-phenol

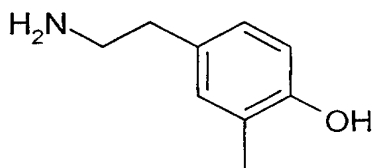
348



Dissolve 2-methyl-4-hydroxy-benzaldehyde (980 mg, 6.3 mmol), nitromethane (2.0 mL, 37.7 mmol) and ammonium acetate (1.9 g, 25.1 mmol) in acetic acid (9 mL). Heat the reaction mixture at 110°C for 2 hours. Concentrate the reaction mixture under reduced pressure and partition the residue between ether and water. Separate the layers and dry with Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate under reduced pressure to afford a crude product. Purify the crude by flash chromatography (eluent: EtOAc/hexane 20/80 and 30/70) to afford the title compound (1.0 g). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): 7.94 (d, 1H, J= 13.4 Hz), 7.50 (d, 1H, J= 13.6 Hz), 7.34-7.27 (m, 2H), 6.82 (d, 1H, J= 8.1 Hz), 2.28 (s, 3H).

## Step 2

## 4-(2-Amino-ethyl)-2-methyl-phenol



Procedure 1: Dissolve compound obtained in step 1 above (440 mg, 2.46 mmol) in methanol (10 mL) and add Pd/C 10% (272 mg) and HCl conc (1 mL). Stir the mixture at room temperature under hydrogen overnight. Filter the mixture over celite and evaporate the solvent to afford a crude product. Purify the crude product by SCX column to obtain the title compound (232 mg, 63%).

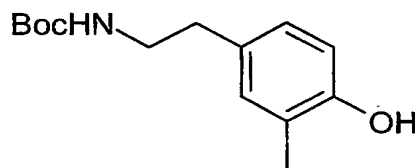
Procedure 2: To lithium aluminum hydride 1.0M in ether (1.67 mL, 1.67 mmol) at 0°C a solution of aluminum trichloride (224 mg, 1.67 mmol) in THF (2 mL) is added. After 5 min a solution of compound obtained in step 1 above (100 mg, 0.56 mmol) in THF (2 mL) is added and the reaction is allowed to stir at room temperature overnight. Add water and then 3 N HCl, the aqueous layer is extracted with 3/1 n-butanol/toluene. The combined organic layers are dried over sodium sulfate and concentrated. SCX ion-exchange chromatography afforded 71 mg (84%) of the title compound. Electrospray MS



M+1 ion= 152. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 6.89 (bs, 1H), 6.82 (dd, 1H, J= 8.3 and 2.4 Hz), 6.64 (d, 1H, J= 8.1 Hz), 2.80 (t, 2H, J= 6.7 Hz), 2.61 (t, 2H, J= 7.0 Hz), 2.15 (s, 3H).

### Step3

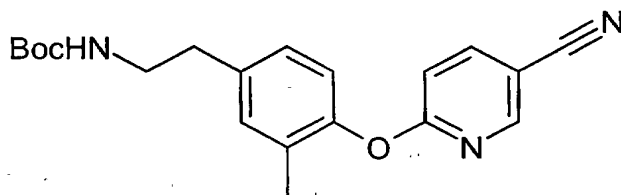
[2-(4-Hydroxy-3-methyl-phenyl)-ethyl]-carbamic acid *tert*-butyl ester



Dissolve amine obtained in step 2 above (289 mg, 1.91 mmol) in dry THF (5 mL) under N<sub>2</sub> atmosphere, add a solution of di-*tert*butyl dicarbonate (439 mg, 2.0 mmol) in THF (5 mL), stir the mixture at room temperature overnight. Evaporate the solvent to obtain the title compound (462 mg, 96%). TLC R<sub>f</sub> (EtOAc/hexane 20/80): 0.27. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 6.88 (bs, 1H), 6.82 (d, 1H, J= 8.3 Hz), 6.63 (d, 1H, J= 8.1 Hz), 3.17 (t, 2H, J= 6.7 Hz), 2.60 (t, 2H, J= 7.0 Hz), 2.14 (s, 3H), 1.50 (s, 9H).

### Step 4

{2-[4-(5-Cyano-pyridin-2-yloxy)-3-methyl-phenyl]-ethyl}-carbamic acid *tert*-butyl ester



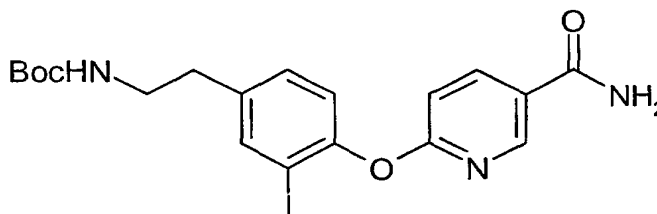
A solution of phenol obtained in step 3 above (455 mg, 1.1 mmol), 6-chloronicotinonitrile (251 mg, 1.81 mmol) and sodium hydride (87 mg, 2.17 mmol) in DMSO (10 mL) is stirred at room temperature for 18 hours. Pour the mixture into ice cold water and extract the aqueous layer with EtOAc. Dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>, filter, and concentrate the filtrate to afford a crude product. Purify the crude product by flash column chromatography (eluent: EtOAc/hexane 15/85 and 20/80) to afford the title compound (358 mg, 57%). Electrospray MS M<sup>+</sup>+1-Boc group ion: 298. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200

350

MHz): 8.42 (dd, 1H, J= 0.5 and 2.4 Hz), 7.90 (dd, 1H, J= 2.4 and 8.6 Hz), 7.11-6.94 (m, 4H), 3.37 (q, 2H, J= 7.0 Hz), 2.77 (t, 2H, J= 7.2 Hz), 2.10 (s, 3H), 1.43 (s, 9H).

## Step 5

{2-[4-(5-Carbamoyl-pyridin-2-yloxy)-3-methyl-phenyl]-ethyl}-carbamic acid *tert*-butyl ester

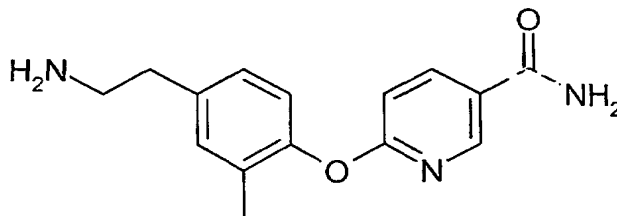


The compound of step 4 is subject to hydrolysis using hydrogen peroxide and potassium carbonate. The details of the hydrolysis procedure to form an amide from the corresponding nitrile have been described previously.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): 8.58 (d, 1H, J= 2.4 Hz), 8.17 (dd, 1H, J= 2.4 and 8.6 Hz), 7.09-6.90 (m, 4H), 3.38 (q, 2H, J= 6.7 Hz), 2.77 (t, 2H, J= 7.0 Hz), 2.11 (s, 3H), 1.43 (s, 9H).

## Step 6

6-[4-(2-Amino-ethyl)-2-methyl-phenoxy]-nicotinamide



To a solution of the compound of step 5 (376 mg, 1.01 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), add trifluoroacetic acid (2.03 mL, 26.4 mmol). Stir the reaction mixture at room temperature for 2 hours. Eliminate the solvent and purify by SCX column to obtain the title compound (264 mg, 96%). Electrospray MS M<sup>+</sup>+1 ion: 272. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.58 (d, 1H, J= 2.4 Hz), 8.24 (dd, 1H, J= 2.7 and 8.9 Hz), 7.17-6.94 (m, 4H), 2.94-2.86 (m, 2H), 2.78-2.71 (m, 2H), 2.10 (s, 3H).

## Step 7

Combine 3-methyl-butylaldehyde (60 $\mu$ l, 0.22 mmol), amine from step 6 above (60 mg, 0.22 mmol) and 3A molecular sieves (670 mg) in methanol (2 mL), stir the mixture at room temperature overnight. Add NaBH<sub>4</sub> (41 mg, 1.10 mmol) and stir at room temperature for 3 hours. Filter the mixture over celite® and concentrate the filtrate to afford a crude product. Purify the crude mixture by flash chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 80/20) to obtain the title compound (45 mg, 60%). Electrospray MS M+1 ion = 342. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.59 (dd, 1H, J= 0.8 and 2.7 Hz), 8.24 (dd, 1H, J= 2.4 and 8.6 Hz), 7.19-7.10 (m, 2H), 7.00-6.93 (m, 2H), 2.93-2.76 (m, 4H), 2.70-2.62 (m, 2H), 2.10 (s, 3H), 1.71-1.36 (m, 3H), 0.91 (d, 6H, J= 6.4 Hz).

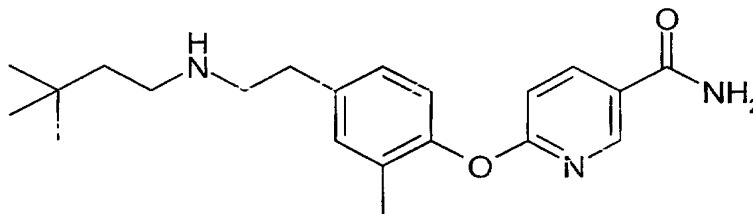
### Examples 546-552

Compounds of examples 546-552 were prepared following the method of example 545.

The purification process is described in each case

#### Example 546

6-{2-Methyl-4-[2-(3,3-dimethyl-butylamino)-ethyl]-phenoxy}-nicotinamide

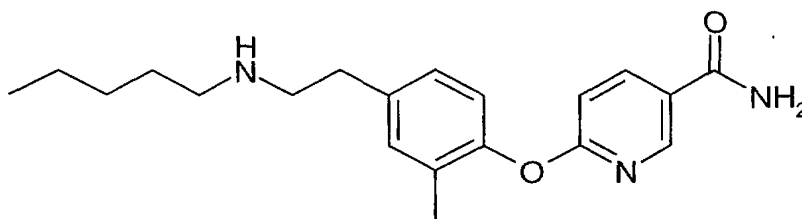


Purification: SCX column. Electrospray MS M+1 ion = 356. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.59 (d, 1H, J= 2.4 Hz), 8.24 (dd, 1H, J= 2.4 and 8.6 Hz), 7.18-7.10 (m, 2H), 7.00-6.94 (m, 2H), 2.92-2.78 (m, 4H), 2.69-2.60 (m, 2H), 2.10 (s, 3H), 1.48-1.39 (m, 2H), 0.93 (s, 9H).

#### Example 547

6-[2-Methyl-4-(2-pentylamino-ethyl)-phenoxy]-nicotinamide

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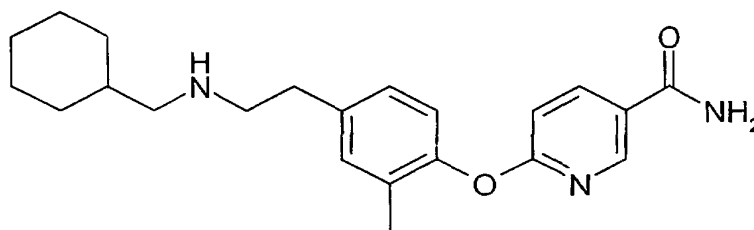


Purification: Flash chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>/EtOAc/MeOH:NH<sub>3</sub> 2M 35/60/5).

Electrospray MS M+1 ion = 342. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.59 (dd, 1H, J= 0.5 and 2.3 Hz), 8.24 (dd, 1H, J= 2.6 and 8.8 Hz), 7.17-7.08 (m, 2H), 6.98-6.92 (m, 2H), 2.88-2.75 (m, 4H), 2.65-2.57 (m, 2H), 2.09 (s, 3H), 1.59-1.25 (m, 6H), 0.91 (t, 3H, J= 6.4 Hz).

#### Example 548

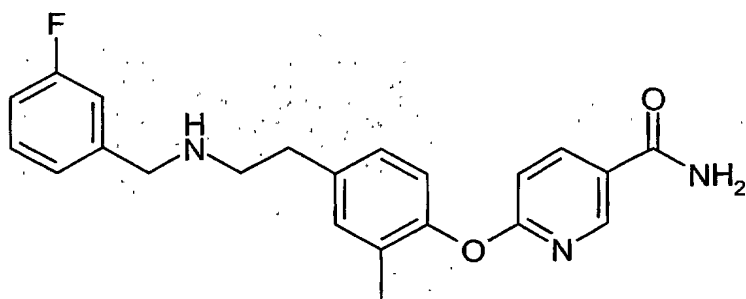
6-{4-[2-(Cyclohexylmethyl-amino)-ethyl]-2-methyl-phenoxy}-nicotinamide



Purification: Flash chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10). Electrospray MS M+1 ion = 368. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.59 (d, 1H, J= 2.4 Hz), 8.24 (dd, 1H, J= 2.7 and 8.6 Hz), 7.18-7.10 (m, 2H), 7.00-6.93 (m, 2H), 2.85 (bs, 4H), 2.50 (d, 2H, J= 6.4 Hz), 2.10 (s, 3H), 1.77-0.84 (m, 11H).

#### Example 549

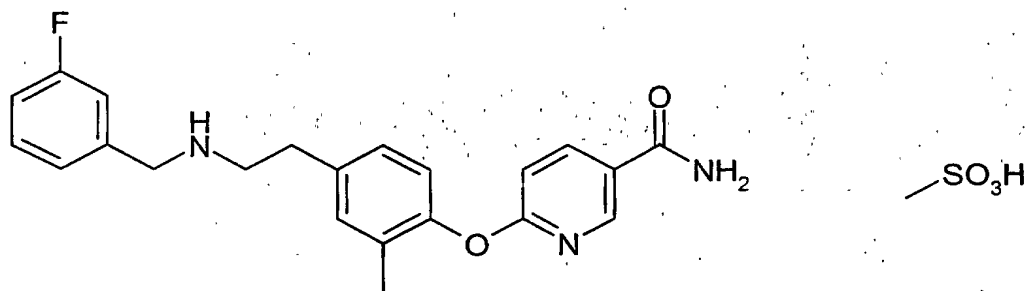
6-{4-[2-(3-Fluoro-benzylamino)-ethyl]-2-methyl-phenoxy}-nicotinamide



Purification: SCX column. Electrospray MS M+1 ion = 380. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.59 (dd, 1H, J= 0.5 and 2.4 Hz), 8.24 (dd, 1H, J= 2.4 and 8.6 Hz), 7.38-6.92 (m, 8H), 3.79 (s, 2H), 2.82 (s, 4H), 2.09 (s, 3H).

#### Example 550

6-{4-[2-(3-Fluorobenzylamino)ethyl]-2-methylphenoxy}-nicotinamide, mesylate salt

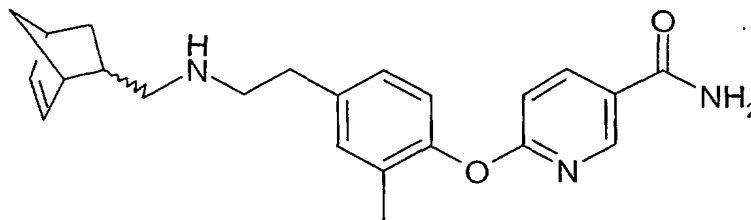


Example 5 (free amine of example 6) was dissolved in THF, then methanesulfonic acid was added (1.0 eq), the mixture was stirred for 1 hour and the solvent eliminated to give the title compound. Electrospray MS M+1 ion = 380. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 300 MHz): 8.59 (bs, 1H), 8.28 (dd, 1H, J= 1.4 and 8.7 Hz), 7.56-7.02 (m, 8H), 4.30 (s, 2H), 3.36 (t, 2H, J= 7.3 Hz), 3.06 (t, 2H, J= 7.3 Hz), 2.72 (s, 3H), 2.14 (s, 3H).

#### Example 551

6-(4-{2-[(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)amino]ethyl}-2-methylphenoxy)-nicotinamide

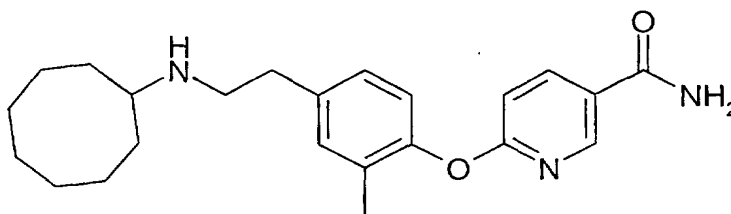
354



Purification: HPLC (Column: X-Terra MS C18. A= 10 Mm  $\text{NH}_4\text{HCO}_3$  pH9/B=  $\text{CH}_3\text{CN}$ . Gradient mode: from 30 to 99% B. Flow rate: 1mL/min). Electrospray MS M+1 ion = 378.  $^1\text{H}$ -NMR (methanol- $d_4$ , 200 MHz): 8.59 (d, 1H,  $J$ = 2.6 Hz), 8.24 (dd, 1H,  $J$ = 2.4 and 8.6 Hz), 7.16-6.91 (m, 4H), 6.16-5.88 (m, 2H), 2.81-1.81 (m, 9H), 2.09 (s, 3H), 1.65-0.99 (m, 3H), 0.57-0.48 (m, 1H).

### Example 552

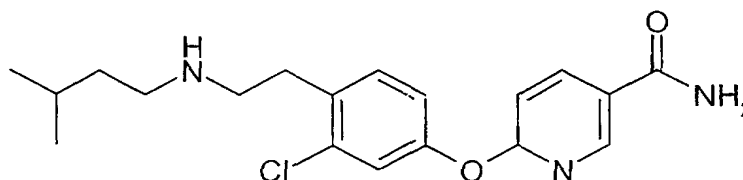
6-[4-(2-Cyclooctylamino-ethyl)-2-methyl-phenoxy]-nicotinamide



Purification: Flash chromatography (eluent:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  70/30). Electrospray MS M+1 ion = 382  $^1\text{H}$ -NMR (methanol- $d_4$ , 200 MHz): 8.59 (d, 1H,  $J$ = 2.4 Hz), 8.24 (dd, 1H,  $J$ = 2.4 and 8.6 Hz), 7.18-6.92 (m, 4H), 2.95-2.77 (m, 5H), 2.12 (m, 1H), 2.10 (s, 3H), 1.89-1.46 (m, 13H).

### Example 553

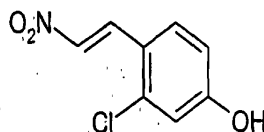
6-{3-Chloro-4-[2-(3-methyl-butylamino)-ethyl]-phenoxy}-nicotinamide



Step 1

3-Chloro-4-(2-nitro-vinyl)-phenol

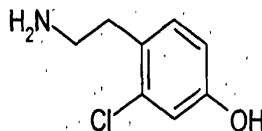
355



The 3-chloro-4-hydroxy-benzaldehyde (980 mg, 6.3 mmol), nitromethane (2.0 mL, 37.7 mmol) and ammonium acetate (1.9 g, 25.1 mmol) were dissolved in acetic acid (9 mL) and the reaction heated at 110°C for 2 hours. The reaction is concentrated under reduced pressure and the residue partitioned between ether and water. Separate the layers and dry with Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate under reduced pressure. Purify the crude product by flash chromatography (eluent: EtOAc/hexane 20/80 and 30/70) afforded the title compound (1.0 g, 80%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): 8.34 (d, 1H, J= 13.4 Hz), 7.82 (d, 1H, J= 13.4 Hz), 7.71 (d, 1H, J= 8.6 Hz), 6.94 (d, 1H, J= 2.4 Hz), 6.80 (dd, 1H, J= 2.4 and 8.6 Hz).

## Step 2

4-(2-Amino-ethyl)-3-chloro-phenol

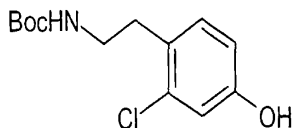


To lithium aluminum hydride 1.0M in ether (1.50 mL, 1.50 mmol) at 0°C a solution of aluminum trichloride (201 mg, 1.51 mmol) in THF (2 mL) is added. After 5 min a solution of compound obtained in step 1 above (100 mg, 0.50 mmol) in THF (2 mL) is added and the reaction is allowed to stir at room temperature overnight. Add water and then 3 N HCl. Extract the aqueous layer with 3/1 n-butanol/toluene. The combined organic layers are dried over sodium sulfate and concentrated. SCX ion-exchange chromatography of the concentrate afforded 70 mg (81%) of the title compound. Electrospray MS M+1 ion= 172. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 7.06 (d, 1H, J= 8.3 Hz), 6.79 (d, 1H, J= 2.4 Hz), 6.65 (dd, 1H, J= 2.4 and 8.3 Hz), 2.82 (m, 4H).

## Step3

[2-(4-Hydroxy-2-chloro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester

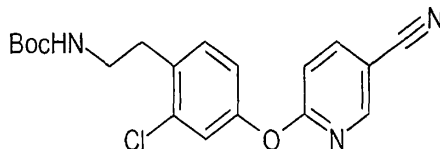
356



Dissolve amine obtained in step 2 above (620 mg, 3.62 mmol) in dry THF (20 mL) and DMF (1 mL) under  $N_2$  atmosphere, add a solution of di-tertbutyl dicarbonate (791 mg, 3.62 mmol) in THF (10 mL), stir the mixture at room temperature overnight. Concentrate the mixture to a crude product and purify the crude product by flash chromatography (eluent: EtOAc/hexane 30/70) to obtain the title compound (670 mg, 68%). TLC  $R_f$  (EtOAc/hexane 20/80): 0.27.  $^1H$ -NMR (methanol- $d_4$ , 200 MHz): 7.06 (d, 1H,  $J$ = 8.3 Hz), 6.78 (d, 1H,  $J$ = 2.6 Hz), 6.65 (dd, 1H,  $J$ = 2.4 and 8.3 Hz), 3.21 (t, 2H,  $J$ = 6.7 Hz), 2.78 (t, 2H,  $J$ = 7.5 Hz), 1.41 (s, 9H).

## Step 4

{2-[4-(5-Cyano-pyridin-2-yloxy)-2-chloro-phenyl]-ethyl}-carbamic acid *tert*-butyl ester



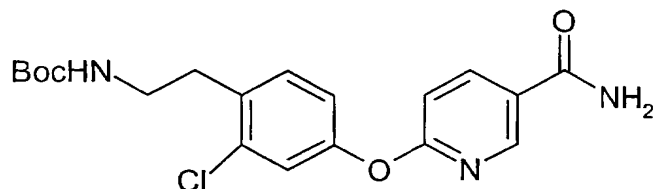
A solution of phenol obtained in step 3 above (650 mg, 2.4 mmol), 6-chloronicotinonitrile (333 mg, 2.4 mmol) and sodium hydride (115 mg, 2.9 mmol) in DMSO (12 mL) is stirred at room temperature for 18 hours. Pour the mixture into cold water (about 0 °C) and extract the aqueous layer with EtOAc. Dry the organic layer over  $Na_2SO_4$ , filter and concentrate the filtrate to afford a crude product. Purify the crude product by flash chromatography (eluent: EtOAc/hexane 20/80 and 30/70) to afford the title compound (810 mg, 90%). Electrospray MS  $M^+ + 1$ -Boc group ion: 318.  $^1H$ -NMR ( $CDCl_3$ , 200 MHz): 8.46 (dd, 1H,  $J$ = 0.5 and 2.2 Hz), 7.94 (dd, 1H,  $J$ = 2.4 and 8.6 Hz), 7.31-7.18 (m, 2H), 7.06-6.98 (m, 2H), 3.41 (q, 2H,  $J$ = 6.7 Hz), 2.95 (t, 2H,  $J$ = 7.3 Hz), 1.44 (s, 9H).

## Step 5

{2-[4-(5-Carbamoyl-pyridin-2-yloxy)-2-chloro-phenyl]-ethyl}-carbamic acid *tert*-butyl ester



357

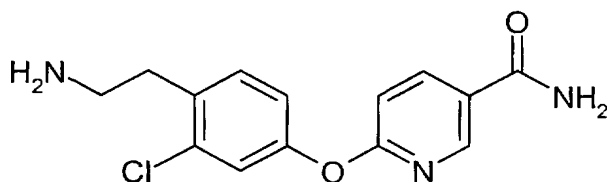


The compound of step 4 is subject to hydrolysis using hydrogen peroxide and potassium carbonate. The details of the hydrolysis procedure to form analogous amides from the corresponding nitrile have been described previously.

$^1\text{H-NMR}$  (methanol- $\text{d}_4$ , 200 MHz): 8.62 (dd, 1H,  $J=0.8$  and 2.7 Hz), 8.27 (dd, 1H,  $J=2.4$  and 8.6 Hz), 7.34 (d, 1H,  $J=8.3$  Hz), 7.22 (d, 1H,  $J=2.4$  Hz), 7.07-7.02 (m, 2H), 3.34 (m, 2H), 2.92 (t, 2H,  $J=7.3$  Hz), 1.42 (s, 9H).

#### Step 6

6-[4-(2-Amino-ethyl)-2-chloro-phenoxy]-nicotinamide



The compound of step 5 is subjected to hydrolysis using trifluoroacetic acid. The details of the hydrolysis procedure to remove the protecting group have been described previously. Electrospray MS  $\text{M}+1$  ion = 292.  $^1\text{H-NMR}$  (methanol- $\text{d}_4$ , 200 MHz): 8.60 (dd, 1H,  $J=0.8$  and 2.7 Hz), 8.28 (dd, 1H,  $J=2.7$  and 8.9 Hz), 7.38 (d, 1H,  $J=8.3$  Hz), 7.24 (d, 1H,  $J=2.4$  Hz), 7.09-7.03 (m, 2H), 2.94 (s, 4H).

#### Step 7

Combine compound from step 6 (60mg, 0.21 mmol), 3-methyl-butyraldehyde (24  $\mu\text{L}$ , 0.23 mmol) and 3A molecular sieves (670 mg) in methanol (2 mL), stir the mixture at room temperature overnight. Add  $\text{NaBH}_4$  (41 mg, 1.10 mmol) and stir at room temperature for 3 hours. Filter the mixture over celite. Concentrate the filtrate to afford the crude product. Purify the crude product using an SCX column to obtain the title compound. Electrospray MS  $\text{M}+1$  ion = 362.  $^1\text{H-NMR}$  (methanol- $\text{d}_4$ , 200 MHz): 8.61 (dd, 1H,  $J=0.8$  and 2.7 Hz),

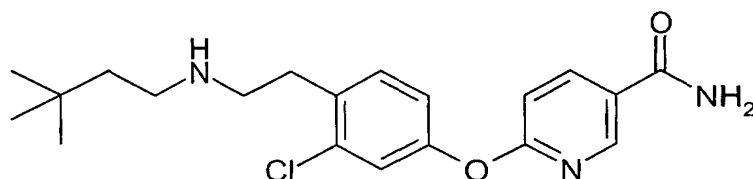
8.27 (dd, 1H, J= 2.4 and 8.6 Hz), 7.38 (d, 1H, J= 8.6 Hz), 7.22 (d, 1H, J= 2.4 Hz), 7.07-7.03 (m, 2H), 3.03-2.81 (m, 4H), 2.70-2.62 (m, 2H), 1.62 (m, 1H), 1.48-1.37 (m, 2H), 0.92 (d, 6H, J= 6.5 Hz).

### Examples 554-558

Compounds of examples 554-558 were prepared following procedures similar to that of Example 553. The purification process is described in each case.

#### Example 554

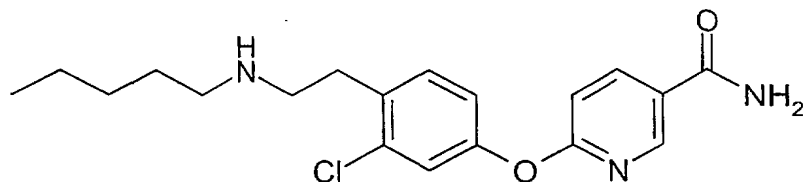
6-{3-Chloro-4-[2-(3,3-dimethyl-butylamino)-ethyl]-phenoxy}-nicotinamide



Purification: SCX column. Electrospray MS M+1 ion = 376. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.61 (dd, 1H, J= 0.5 and 2.4 Hz), 8.27 (dd, 1H, J= 2.7 and 8.9 Hz), 7.38 (d, 1H, J= 8.3 Hz), 7.22 (d, 1H, J= 2.4 Hz), 7.09-7.03 (m, 2H), 3.02-2.81 (m, 4H), 2.69-2.61 (m, 2H), 1.49-1.40 (m, 2H), 0.93 (s, 9H).

#### Example 555

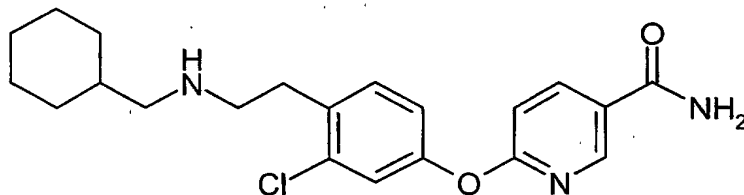
6-[3-Chloro-4-(2-pentylamino-ethyl)-phenoxy]-nicotinamide



Purification: flash chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10). Electrospray MS M+1 ion = 362. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.61 (dd, 1H, J= 0.8 and 2.4 Hz), 8.27 (dd, 1H, J= 2.4 and 8.6 Hz), 7.38 (d, 1H, J= 8.3 Hz), 7.23 (d, 1H, J= 2.4 Hz), 7.09-7.03 (m, 2H), 3.03-2.81 (m, 4H), 2.68-2.61 (m, 2H), 1.61-1.47 (m, 2H), 1.37-1.28 (m, 4H), 0.93 (t, 3H, J= 6.7 Hz).

**Example 556**

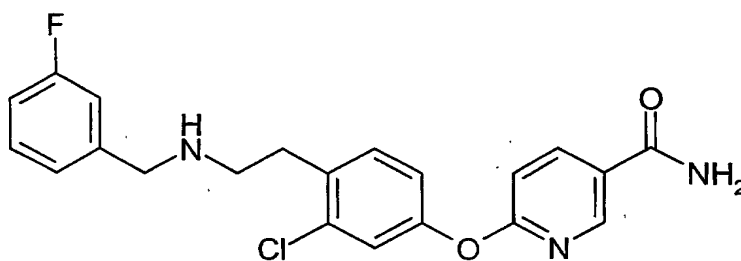
6-{3-Chloro-4-[2-(cyclohexylmethyl-amino)-ethyl]-phenoxy}-nicotinamide



Purification: SCX column. Electrospray MS M+1 ion = 388. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 300 MHz): 8.63 (d, 1H, J= 1.8 Hz), 8.28 (dd, 1H, J= 2.4 and 8.5 Hz), 7.37 (d, 1H, J= 8.2 Hz), 7.22 (d, 1H, J= 2.2 Hz), 7.07-7.03 (m, 2H), 3.01-2.81 (m, 4H), 2.49 (d, 2H, J= 6.7 Hz), 1.79-1.68 (m, 5H), 1.61-1.42 (m, 1H), 1.38-1.17 (m, 3H), 0.99- 0.85 (m, 2H).

**Example 557**

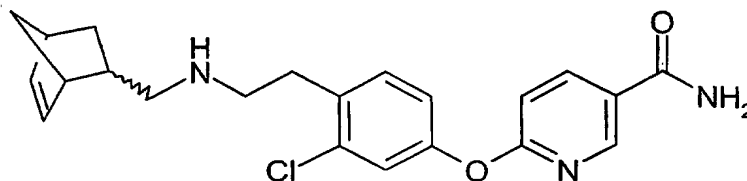
6-{3-Chloro-4-[2-(3-fluorobenzylamino)-ethyl]-phenoxy}-nicotinamide



Purification: SCX column. Electrospray MS M+1 ion = 400. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 300 MHz): 8.63 (d, 1H, J= 2.2 Hz), 8.27 (dd, 1H, J= 2.4 and 8.7 Hz), 7.36-6.95 (m, 8H), 3.82 (s, 2H), 3.01-2.81 (m, 4H).

**Example 558**

6-(4-{2-[(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-ethyl}-3-chloro-phenoxy)-nicotinamide



nicotinamide

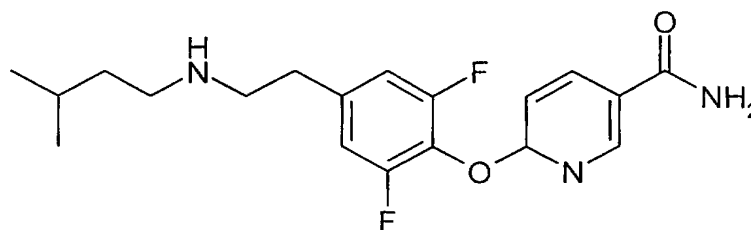
Purification: SCX column. Electrospray MS M+1 ion = 398. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.61 (dd, 1H, J= 0.5 and 2.4 Hz), 8.26 (dd, 1H, J= 2.4 and 8.6 Hz), 7.40-7.03 (m,

360

4H), 6.18-5.92 (m, 2H), 3.01-2.66 (m, 6H), 2.40-2.18 (m, 2H), 1.95-1.83 (m, 1H), 1.64-1.11 (m, 3H), 0.60-0.50 (m, 1H).

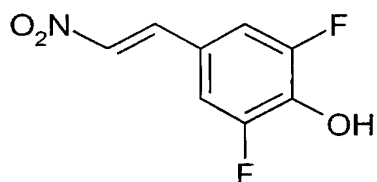
**Example 559**

6-{2,6-Difluoro-4-[2-(3-methyl-butylamino)-ethyl]-phenoxy}-nicotinamide



Step 1

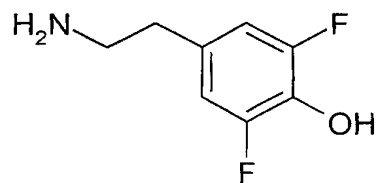
2,6-Difluoro-4-(2-nitro-vinyl)-phenol



3,5-Difluoro-4-hydroxybenzaldehyde (2.27g, 14.4 mmol), nitromethane (4.7 mL, 86.4 mmol) and ammonium acetate (4.4 g, 57.6 mmol) were dissolved in acetic acid (22 mL) and the reaction mixture was heated at 110°C for 1 hour 30 min. The reaction was concentrated under reduced pressure and the residue partitioned between ether and water. the layers were separated and the organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>. The organic mixture was filtered and the filtrate concentrated under reduced pressure to afford a crude product. The crude product was purified by flash column chromatography (eluent: EtOAc/hexane 22/78) to afford the title compound (2.05 g, yield: 71%). Electrospray MS M-1 ion = 200. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): 7.84 (d, 1H, J= 13.7 Hz), 7.45 (d, 1H, J= 13.7 Hz), 7.19-6.99 (m, 2H).

Step 2

4-(2-Amino-ethyl)-2,6-difluoro-phenol

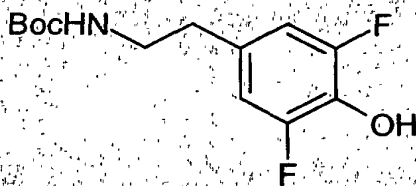


361

To lithium aluminum hydride 1.0M in ether (30 mL, 29.8 mmol) at 0°C a solution of aluminum trichloride (4.0g, 29.8 mmol) in THF (40 mL) is added. After 5 min a solution of compound obtained in step 1 above (2.0g, 9.95 mmol) in THF (40 mL) is added and the reaction is allowed to stir at room temperature overnight. Add water and then 3 N HCL, the aqueous layer is extracted with 3/1 n-butanol/toluene. The combined organic layers are dried over sodium sulfate and concentrated. SCX ion-exchange chromatography afforded 1.50 g (87%) of the title compound. Electrospray MS M+1-ion= 174. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 6.95-6.78 (m, 2H), 3.14 (t, 2H, J= 7.0 Hz), 2.86 (t, 2H, J= 7.3 Hz).

## Step 3

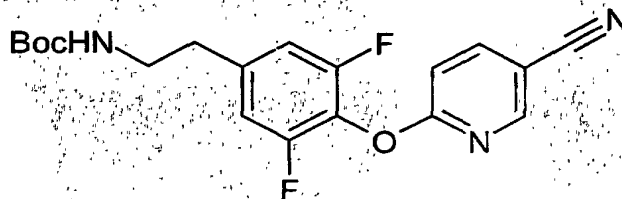
[2-(3,5-Difluoro-4-hydroxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester



Dissolve amine obtained in step 2 above (1.5 g, 8.67 mmol) in dry THF (22 mL) under N<sub>2</sub> atmosphere, add a solution of di-*tert*butyl dicarbonate (1.89 g, 8.67 mmol) in THF (22 mL), stir the mixture at room temperature overnight. Eliminate the solven. Purify by flash chromatography (eluent: EtOAc/hexane 1/4 and 1/1) to obtain the desired compound (1.40 g). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): 6.85-6.66 (m, 2H), 3.31 (q, 2H, J= 6.2 Hz), 2.69 (t, 2H, J= 7.0 Hz), 1.44 (s, 9H).

## Step 4

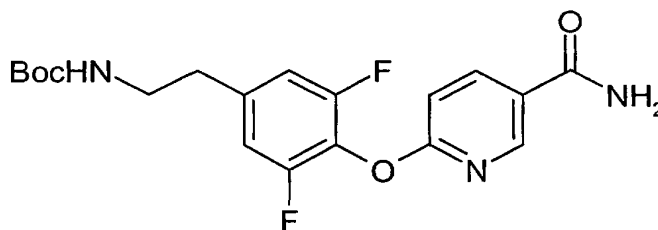
{2-[4-(5-Cyano-pyridin-2-yloxy)-3,5-difluoro-phenyl]-ethyl}-carbamic acid *tert*-butyl ester



A solution of phenol obtained in step 3 above (1.31 g, 4.8 mmol), 6-chloronicotinonitrile (700 mg, 5.04 mmol) and sodium hydride (290 mg, 7.2 mmol) in DMSO (25 mL) is stirred at room temperature for 18 hours. Pour the mixture into iced water and extract the aqueous layer with EtOAc. Dry the organic layer over  $\text{Na}_2\text{SO}_4$ , filtrate and eliminate the solvent. Purify by flash chromatography (EtOAc/hexane 20/80 and 34/66) to get the title compound (950 mg, 51%).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz): 8.41 (dd, 1H,  $J=0.8$  and 2.1 Hz), 7.97 (dd, 1H,  $J=2.4$  and 8.6 Hz), 7.18 (dd, 1H,  $J=0.8$  and 8.6 Hz), 6.92-6.81 (m, 2H), 3.39 (q, 2H,  $J=6.9$  Hz), 2.81 (t, 2H,  $J=6.7$  Hz), 1.45 (s, 9H).

## Step 5

{2-[4-(5-Carbamoyl-pyridin-2-yloxy)-3,5-difluoro-phenyl]-ethyl}-carbamic acid *tert*-butyl ester

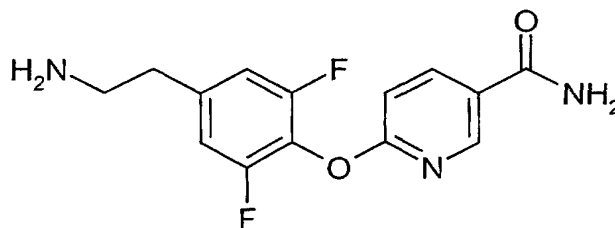


The compound of step 4 is subjected to hydrolysis using hydrogen peroxide and potassium carbonate. The details of the hydrolysis procedure to form analogous amides from the corresponding nitrile have been described previously.

$^1\text{H-NMR}$  (methanol- $\text{d}_4$ , 300 MHz): 8.58 (d, 1H,  $J=2.4$  Hz), 8.31 (dd, 1H,  $J=2.4$  and 8.7 Hz), 7.19 (d, 1H,  $J=8.7$  Hz), 7.02-6.98 (m, 2H), 3.35-3.30 (m, 2H), 2.81 (t, 2H,  $J=7.1$  Hz), 1.44 (s, 9H).

## Step 6

6-[4-(2-Amino-ethyl)-2,6difluoro-phenoxy]-nicotinamide



To a solution of compound of step 5 (930 mg, 2.37 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL), trifluoroacetic acid is added (4.7 mL, 61.5 mmol). Stir the reaction mixture at room temperature for 2h. Eliminate the solvent and purify by SCX column to obtain the title compound (658 mg, 95%). Electrospray MS  $\text{M}^+ + 1$  ion: 294.  $^1\text{H}$ -NMR (methanol- $\text{d}_4$ , 200 MHz): 8.56 (d, 1H,  $J = 2.4$  Hz), 8.30 (dd, 1H,  $J = 2.4$  and 8.9 Hz), 7.18 (d, 1H,  $J = 8.9$  Hz), 7.05-6.95 (m, 2H), 2.96-2.74 (m, 4H).

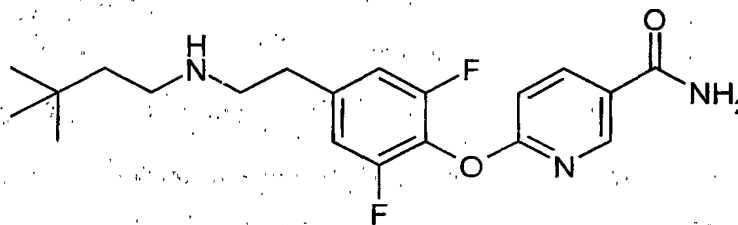
### Step 7

Combine 3-methyl-butylaldehyde (26  $\mu\text{l}$ , 0.24 mmol), amine from step 6 above and 3A molecular sieves (900 mg) in methanol (3 mL), stir the mixture at room temperature overnight. Add  $\text{NaBH}_4$  (45 mg, 1.20 mmol) and stir at room temperature for 3 hours. Filtrate the mixture over celite and eliminate the solvent. Submit the crude to a SCX column to obtain a solid which was further purified by HPLC (Column: X-Terra MS C18. A= 10 Mm  $\text{NH}_4\text{HCO}_3$  pH8/B=  $\text{CH}_3\text{CN}$ . Gradient mode: from 30 to 70% B. Flow rate: 1 mL/min) to obtain the title compound (42 mg). Electrospray MS  $\text{M} + 1$  ion = 364.  $^1\text{H}$ -NMR (methanol- $\text{d}_4$ , 300 MHz): 8.60 (d, 1H,  $J = 2.0$  Hz), 8.32 (dd, 1H,  $J = 2.2$  and 8.5 Hz), 7.19 (d, 1H,  $J = 8.7$  Hz), 7.01-6.98 (m, 2H), 2.85 (m, 4H), 2.63 (m, 2H), 1.62 (m, 1H), 1.42 (q, 1H,  $J = 7.3$  Hz), 0.92 (d, 6H,  $J = 6.5$  Hz).

By the method of example 559 the following examples (examples 560-563) were prepared. The purification process is described in each case

### Example 560

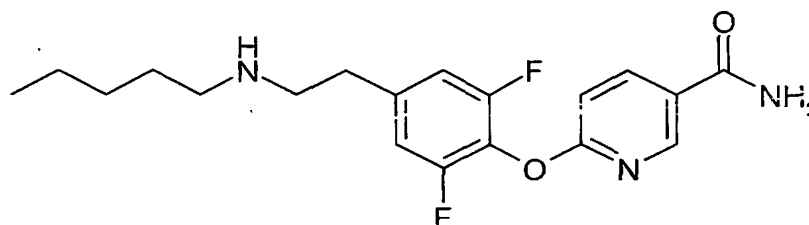
6-{4-[2-(3,3-Dimethyl-butylamino)-ethyl]-2,6-difluoro-phenoxy}-nicotinamide



Purification: HPLC (Column: X-Terra MS C18. A= 10 Mm NH<sub>4</sub>HCO<sub>3</sub> pH8/B= CH<sub>3</sub>CN. Gradient mode: from 30 to 99% B. Flow rate: 1mL/min ). Electrospray MS M+1 ion = 378. <sup>1</sup>H-NMR (metanol-d<sub>4</sub>, 300 MHz): 8.48 (d, 1H, J= 2.4 Hz), 8.23 (dd, 1H, J= 2.4 and 8.5 Hz), 7.12 (d, 1H, J= 8.5 Hz), 7.00-6.93 (m, 2H), 2.91-2.78 (m, 4H), 2.67-2.61 (m, 2H), 1.43-1.38 (m, 2H), 0.87 (s, 9H).

### Example 561

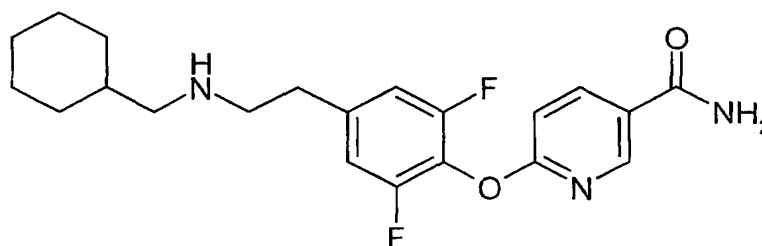
6-[2,6-Difluoro-4-(2-pentylamino-ethyl)-phenoxy]-nicotinamide



Purification: HPLC (Column: X-Terra MS C18. A= 10 Mm NH<sub>4</sub>HCO<sub>3</sub> pH8/B= CH<sub>3</sub>CN. Gradient mode: from 25 to 70% B. Flow rate: 1mL/min). Electrospray MS M+1 ion = 364. <sup>1</sup>H-NMR (metanol-d<sub>4</sub>, 300 MHz): 8.59 (d, 1H, J= 2.4 Hz), 8.32 (dd, 1H, J= 2.4 and 8.7 Hz), 7.19 (d, 1H, J= 8.7 Hz), 7.02-7.00 (m, 2H), 2.88 (m, 4H), 2.65 (t, 2H, J= 7.3 Hz), 1.55 (m, 2H), 1.35 (m, 4H), 0.93 (t, 3H, J= 6.7 Hz).

### Example 562

6-{4-[2-(Cyclohexylmethyl-amino)-ethyl]-2,6-difluoro-phenoxy}-nicotinamide

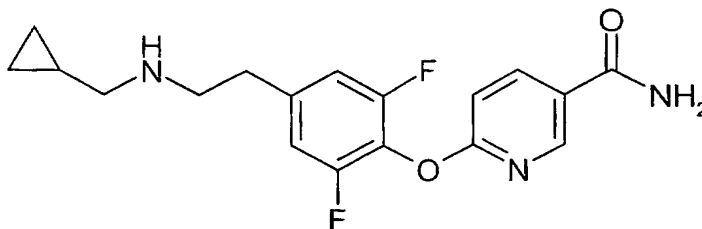


Purification: HPLC (Column: X-Terra MS C18. A= 10 Mm NH<sub>4</sub>HCO<sub>3</sub> pH8/B= CH<sub>3</sub>CN. Gradient mode: from 30 to 99% B. Flow rate: 1mL/min). Electrospray MS M+1 ion = 390. <sup>1</sup>H-NMR (metanol-d<sub>4</sub>, 300 MHz): 8.48 (d, 1H, J= 2.4 Hz), 8.23 (dd, 1H, J= 2.4 and 8.9 Hz), 7.11 (d, 1H, J= 8.8 Hz), 6.99-6.92 (m, 2H), 2.83 (m, 4H), 2.47 (d, 2H, J= 6.9 Hz), 1.72-1.59 (m, 5H), 1.55-1.41 (m, 1H), 1.31-1.05 (m, 3H), 0.94-0.81 (m, 2H).

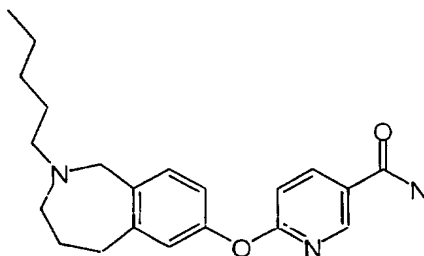


**Example 563**

6-{4-[2-(Cyclopropylmethyl-amino)-ethyl]-2,6-difluoro-phenoxy}-nicotinamide



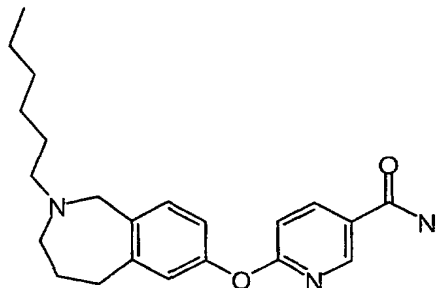
Purification: HPLC (Column: X-Terra MS C18. A= 10 Mm  $\text{NH}_4\text{HCO}_3$  pH8/B= MeOH. Gradient mode: from 35 to 80% B. Flow rate: 1mL/min). Electrospray MS M+1 ion = 348.  $^1\text{H}$ -NMR (methanol- $d_4$ , 300 MHz): 8.59 (d, 1H, J= 2.4 Hz). 8.32 (dd, 1H, J= 2.4 and 8.7 Hz), 7.19 (d, 1H, J= 8.7 Hz), 7.02-7.00 (m, 2H), 2.93-2.83 (m, 4H), 2.50 (d, 2H, J= 6.9 Hz), 1.10-0.90 (m, 1H), 0.55-0.49 (m, 2H), 0.20-0.15 (m, 2H).

**Example 564**6-(2-Pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide

Mix 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide (Example 447, Part E. 0.300 g, 1.06 mmol),  $\text{K}_2\text{CO}_3$  (0.366 g, 2.65 mmol), and 1-bromopentane (0.176 g, 1.16 mmol) in DMF (5.3 mL). Heat at 70 °C overnight and then increase the temperature to 100 °C for additional two hours. Cool the reaction mixture to room temperature and add ethyl acetate (150 mL). Wash with 1.0 N NaOH (1 X 50 mL), brine (1 X 50 mL), dry the organic layer over  $\text{Na}_2\text{SO}_4$ , filter and concentrate. Purify by flash chromatography eluting with 7% to 15% (2.0 M  $\text{NH}_3$  in methanol) in ethyl acetate to give the title compound : MS  $\text{ES}^+$  354.2 ( $\text{M}+\text{H}^+$ ), HRMS calcd for  $\text{C}_{21}\text{H}_{28}\text{N}_3\text{O}_2$  354.2182 ( $\text{M}+\text{H}^+$ ), found 354.2188, time 0.53 min; Anal. Calcd for  $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_2$ : C, 71.36; H, 7.70 N, 11.89. Found: C, 71.14; H, 7.60; N, 11.79.

**Example 565**

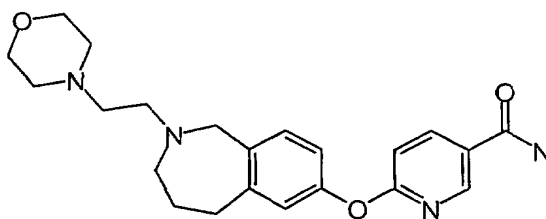
6-(2-Hexyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide



Mix 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide (Example 447, Part E, 0.300 g, 1.06 mmol), K<sub>2</sub>CO<sub>3</sub> (0.366 g, 2.65 mmol), and 1-bromohexane (0.192 g, 1.16 mmol) in DMF (5.3 mL). Heat at 70 °C overnight, then increase the temperature to 100 °C for additional two hours. Cool the reaction mixture to room temperature and add ethyl acetate (150 mL). Wash with 1.0 N NaOH (1 X 50 mL), brine (1 X 50 mL), dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. Purify by flash chromatography eluting with 7% to 15% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound : MS ES<sup>+</sup> 368.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>22</sub>H<sub>30</sub>N<sub>3</sub>O<sub>2</sub> 368.2338 (M+H)<sup>+</sup>, found 368.2334, time 0.53 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18 min], t<sub>R</sub> = 11.6 min, 97.8% purity.

**Example 566**

6-[2-(2-Morpholin-4-ylethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy]nicotinamide

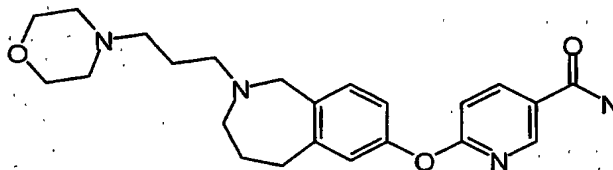


Mix 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide (Example 447, Part E, 0.300 g, 1.06 mmol), K<sub>2</sub>CO<sub>3</sub> (0.366 g, 2.65 mmol), and 4-(2-chloroethyl)morpholine hydrochloride (0.217 g, 1.16 mmol) in DMF (5.3 mL). Heat at 90 °C overnight. Cool the reaction mixture to room temperature and add ethyl acetate

(150 mL). Wash with 1.0 N NaOH (1 X 50 mL), brine (1 X 50 mL), dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. Purify by flash chromatography eluting with 10% to 20% (2.0 M NH<sub>3</sub> in methanol) in acetone to give the title compound : MS ES<sup>+</sup> 397.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>22</sub>H<sub>29</sub>N<sub>4</sub>O<sub>3</sub> 397.2240 (M+H)<sup>+</sup>, found 397.2223, time 0.48 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18 min], t<sub>R</sub> = 5.6 min, 99.0% purity.

### Example 567

6-[2-(3-Morpholin-4-ylpropyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy]nicotinamide

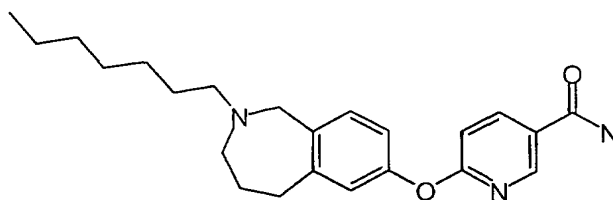


Mix 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide (Example 447, Part E, 0.300 g, 1.06 mmol), K<sub>2</sub>CO<sub>3</sub> (0.366 g, 2.65 mmol), and 4-(3-chloropropyl)morpholine (0.191 g, 1.16 mmol) in DMF (5.3 mL). Heat at 90 °C overnight. Cool the reaction mixture to room temperature and add ethyl acetate (150 mL). Wash with 1.0 N NaOH (1 X 50 mL), brine (1 X 50 mL), dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. Purify by flash chromatography eluting with 10% (2.0 M NH<sub>3</sub> in methanol) in acetone to give the title compound : MS ES<sup>+</sup> 411.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>23</sub>H<sub>31</sub>N<sub>4</sub>O<sub>3</sub> 411.2396 (M+H)<sup>+</sup>, found 411.2389, time 0.48 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18 min], t<sub>R</sub> = 5.7 min, 100% purity.

### Example 568

6-(2-Heptyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide

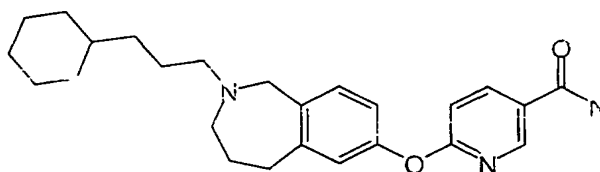
368



Mix 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide (Example 447, Part E, 0.300 g, 1.06 mmol), K<sub>2</sub>CO<sub>3</sub> (0.366 g, 2.65 mmol), and 1-bromoheptane (0.199 g, 1.11 mmol) in DMF (5.3 mL). Heat at 50 °C overnight, then increase the temperature to 80 °C for 3.5 hours. Cool the reaction mixture to room temperature and add ethyl acetate (100 mL). Wash with water (1 X 30 mL), brine (1 X 30 mL), dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. Purify by flash chromatography eluting with 6% to 15% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound : MS ES<sup>+</sup> 382.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>23</sub>H<sub>32</sub>N<sub>3</sub>O<sub>2</sub> 382.2495 (M+H)<sup>+</sup>, found 382.2489, time 0.46 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18 min], t<sub>R</sub> = 12.6 min, 98.6% purity.

#### Example 569

6-[2-(3-Cyclohexylpropyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy]nicotinamide

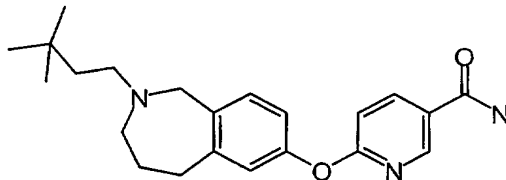


Mix 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide (Example 447, Part E, 0.300 g, 1.06 mmol), K<sub>2</sub>CO<sub>3</sub> (0.366 g, 2.65 mmol), and (3-chloropropyl)cyclohexane (0.179 g, 1.11 mmol) in DMF (5.3 mL). Heat at 50 °C overnight, then increase the temperature to 80 °C for 3.5 hours. Cool the reaction mixture to room temperature and add ethyl acetate (100 mL). Wash with water (1 X 30 mL), brine (1 X 30 mL), dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. Purify by flash chromatography eluting with 6% to 15% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound : MS ES<sup>+</sup> 408.3 (M+H)<sup>+</sup>, HRMS calcd for C<sub>25</sub>H<sub>34</sub>N<sub>3</sub>O<sub>2</sub> 408.2651 (M+H)<sup>+</sup>, found 408.2652, time 0.46 min; HPLC [YMC-Pro pack C-18 (150 x

4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18 min],  $t_R$  = 13.3 min, 100% purity.

### Example 570

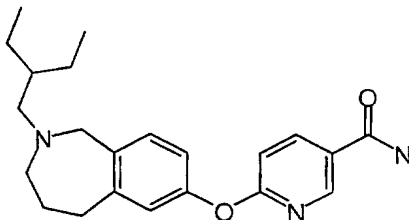
6-[2-(3,3-Dimethylbutyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy]nicotinamide



Mix 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide (Example 447, Part E, 0.300 g, 1.06 mmol),  $K_2CO_3$  (0.366 g, 2.65 mmol), and 1-bromo-3,3-dimethylbutane (0.183 g, 1.11 mmol) in DMF (5.3 mL). Heat at 70 °C overnight. Cool the reaction mixture to room temperature and add ethyl acetate (100 mL). Wash with water (1 X 30 mL) and brine (1 X 30 mL). Dry the organic layer over  $Na_2SO_4$ , filter and concentrate. Purify by flash chromatography eluting with 6% to 15% (2.0 M  $NH_3$  in methanol) in ethyl acetate to give the title compound : MS  $ES^+$  368.2 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{22}H_{30}N_3O_2$  368.2338 ( $M+H$ ) $^+$ , found 368.2321, time 0.53 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18 min],  $t_R$  = 11.1 min, 96.8% purity.

### Example 571

6-[2-(2-Ethylbutyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy]nicotinamide

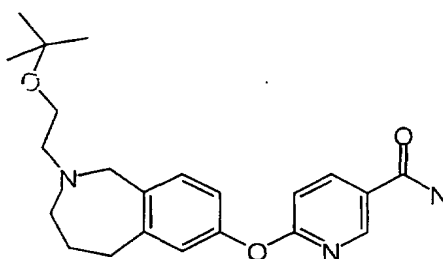


Mix 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide (Example 447, Part E, 0.300 g, 1.06 mmol),  $K_2CO_3$  (0.366 g, 2.65 mmol), and 3-bromomethylpentane (0.183 g, 1.11 mmol) in DMF (5.3 mL). Heat at 70 °C overnight. Cool the reaction mixture to room temperature and add ethyl acetate (100 mL). Wash with water (1 X 30 mL) and brine (1 X 30 mL). Dry the organic layer over  $Na_2SO_4$ , filter

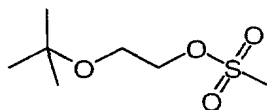
and concentrate. Purify by flash chromatography eluting with 6% to 15% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound : MS ES<sup>+</sup> 368.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>22</sub>H<sub>30</sub>N<sub>3</sub>O<sub>2</sub> 368.2338 (M+H)<sup>+</sup>, found 368.2324, time 0.55 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18 min], t<sub>R</sub> = 10.9 min, 100% purity.

### Example 572

6-[2-(2-*tert*-Butoxyethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy]nicotinamide

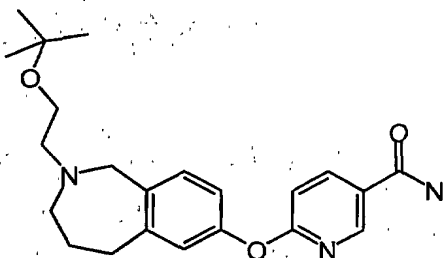


Part A: 2-*tert*-Butoxyethyl methanesulfonate



At 0 °C add triethylamine (35.4 mL, 254 mmol) to a stirring solution of 2-*tert*-butoxyethanol (10.0 g, 84.6 mmol) and methanesulfonic chloride (13.1 mL, 169 mmol) in dichloromethane (169 mL). Allow the reaction mixture to warm to room temperature over night. Dilute the reaction mixture with dichloromethane (200 mL) and wash it with water (1 X 100 mL), 1.0 N HCl (1 X 100 mL) and 1.0 N NaOH (1 X 100 mL). Dry the organic layer over MgSO<sub>4</sub>, filter and concentrate to give the title compound: <sup>1</sup>H NMR (CHCl<sub>3</sub>-*d*<sub>6</sub>) 4.33 (t, 2H), 3.62 (t, 2H), 3.06 (s, 3H), 1.21 (s, 9H); GC/MS, t<sub>R</sub> 13.7 min, % of total 92.9%.

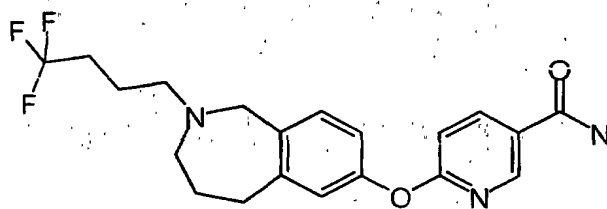
Part B: 6-[2-(2-*tert*-Butoxyethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy]nicotinamide



Mix 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide (Example 447, Part E, 0.300 g, 1.06 mmol),  $K_2CO_3$  (0.366 g, 2.65 mmol), and 2-*tert*-butoxyethyl methanesulfonate (0.218 g, 1.11 mmol) in DMF (5.3 mL). Heat at 70 °C overnight. Cool the reaction mixture to room temperature and add ethyl acetate (100 mL). Wash with water (1 X 30 mL) and brine (1 X 30 mL). Dry the organic layer over  $Na_2SO_4$ , filter and concentrate. Purify by flash chromatography eluting with 6% to 15% (2.0 M  $NH_3$  in methanol) in ethyl acetate to give the title compound: MS  $ES^+$  384.2 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{22}H_{30}N_3O_3$  384.2287 ( $M+H$ ) $^+$ , found 384.2276, time 0.55 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18 min],  $t_R$  = 10.5 min, 97.7% purity.

### Example 573

6-[2-(4,4,4-Trifluorobutyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy]nicotinamide

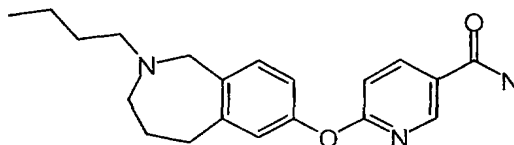


Mix 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide (Example 447, Part E, 0.350 g, 1.24 mmol),  $K_2CO_3$  (0.427 g, 3.09 mmol), and 4-bromo-1,1,1-trifluorobutane (0.248 g, 1.30 mmol) in DMF (6.2 mL). Heat at 95 °C for 5.5 hours, then at 50 °C overnight. Cool the reaction mixture to room temperature and add ethyl acetate (100 mL). Wash with water (1 X 30 mL) and brine (1 X 30 mL). Dry the organic layer over  $Na_2SO_4$ , filter and concentrate. Purify by flash chromatography eluting with 6% to 20% (2.0 M  $NH_3$  in methanol) in ethyl acetate to give the title compound: MS  $ES^+$  394.2 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{20}H_{23}N_3O_2F_3$  394.1742 ( $M+H$ ) $^+$ , found 394.1733, time 0.53 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile

in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18 min],  $t_R$  = 10.1 min, 100% purity.

### Example 574

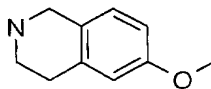
6-(2-Butyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide



Mix 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide (Example 447, Part E, 0.350 g, 1.24 mmol),  $K_2CO_3$  (0.427 g, 3.09 mmol), and 1-bromobutane (0.178 g, 1.30 mmol) in DMF (6.2 mL). Heat at 95 °C for 5.5 hours, then at 50 °C overnight. Cool the reaction mixture to room temperature and add ethyl acetate (100 mL). Wash with water (1 X 30 mL) and brine (1 X 30 mL). Dry the organic layer over  $Na_2SO_4$ , filter and concentrate. Purify by flash chromatography eluting with 6% to 20% (2.0 M  $NH_3$  in methanol) in ethyl acetate to give the title compound : MS  $ES^+$  340.2 ( $M+H$ ) $^+$ , HRMS calcd for  $C_{20}H_{26}N_3O_2$  340.2025 ( $M+H$ ) $^+$ , found 340.2019, time 0.53 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18 min],  $t_R$  = 9.6 min, 98.3% purity.

### Intermediates for Examples 575-578

#### Intermediate 1A



6-Methoxy-1,2,3,4-tetrahydro-isoquinoline

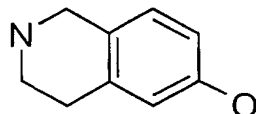
Combine 2-(3-methoxyphenol)ethylamine (10.0 g, 66.13 mmol), 88% Formic acid, and paraformaldehyde (2.05 g, 68.25 mmol) at 0 °C. Stir at room temperature for 24 hours and concentrate under reduced pressure. Add acetyl chloride (5 mL) in MeOH (80 mL) at room temperature and stir for 10 minutes. After concentration, triturate the reaction mixture with ethyl acetate, cool to room temperature, and filter to afford 8.76g, 53.7 mmol (81% yield) of the title compound as a white solid:  $^1H$  NMR (500 MHz,



CD<sub>3</sub>OD); 3.05-13.15 (2H, m), 3.45-3.55 (2H, m), 3.70 (3H, s), 4.30 (2H, s), 4.8-5.0 (1H, br s), 6.8-6.9 (2H, m), 7.1-7.2 (1H, m); MS *m/z* 163 (M<sup>+</sup>).

#### Intermediate 2A

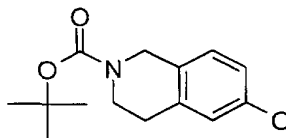
6-Hydroxy-1,2,3,4-tetrahydro-isoquinoline NF7-AOO344-183



Combine 6-methoxy-1,2,3,4-tetrahydro-isoquinoline (5.0 g, 20.5 mmol) and 48% aq HBr (20 mL) at room temperature. Heat the reaction at reflux for 24 hours. cool the reaction to room temperature, and concentrate under reduced pressure. Triturate with ethyl acetate and filter to afford 5.5 g, 20.5 mmol (99% yield) of the title compound as a tan solid: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>); 2.8-2.9 (2H, m), 3.3-3.4 (2H, m), 4.1 (2H, s), 6.5-6.7 (2H, m), 6.9-7.1 (1H, m), 8.8-9.0 (2H, br s), 9.4-9.5 (1H, s).

#### Intermediate 3A

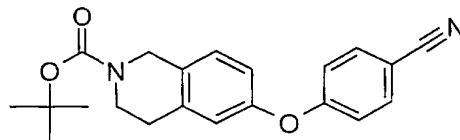
6-Hydroxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester



Combine 6-hydroxy-1,2,3,4-tetrahydroisoquinoline (5.5 g, 23.9 mmol), THF (100 mL), Et<sub>3</sub>N (8.3 mL, 59.8 mmol), and BOC-anhydride (8.3 g, 28.7 mmol). Stir at room temperature for 72 hours under nitrogen, concentrate under reduced pressure and then flash chromatograph using 1:1 hexanes:ethyl acetate eluent to afford 3.51 g, 14.1 mmol (59% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.5 (9H, br s), 2.7-2.8 (2H, m), 3.5-3.6 (2H, m), 4.4 (2H, s), 6.5-6.8 (2H, m), 6.9-7.0 (1H, m); MS *m/z* 150 (M+1-CO<sub>2</sub>*t*-Bu).

## Intermediate 4A

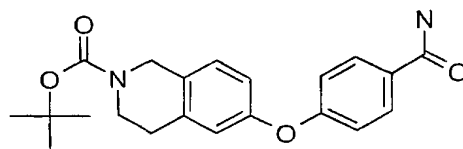
6-(4-Cyano-phenoxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester



Combine in a round bottom flask equipped with a Dean Stark trap 6-hydroxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (1.59 g, 6.36 mmol), toluene, dimethylacetamide (10 mL and 30 mL respectively),  $K_2CO_3$  (1.25 g, 9.04 mmol), and 4-fluorobenzonitrile (0.72 g, 6.04 mmol). Reflux the reaction under a nitrogen atmosphere for 4 hours then cool to room temperature. Add water to the reaction mixture and extract the product from the water layer using ethyl acetate. The product, a white solid, precipitates out from the ethyl acetate to afford 1.93 g, 5.5 mmol (87% yield) of the title compound:  $^1H$  NMR (500 MHz,  $CDCl_3$ ); 1.5 (9H, s), 2.75-2.85 (2H, m), 3.6-3.7 (2H, m), 4.5 (2H, s), 6.8-6.9 (2H, m), 6.9-7.0 (2H, m), 7.1-7.2 (1H, m), 7.5-7.6 (2H, m); MS  $m/z$  249 (M-CO<sub>2</sub>*t*-Bu).

## Intermediate 5A

6-(4-Carbamoyl-phenoxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester  
NF7-AOO344-181

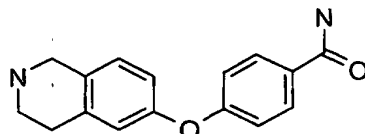


Combine 6-(4-cyano-phenoxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (1.93 g, 5.51 mmol), *t*-butyl alcohol (50 mL), and KOH (1.56 g, 27.6 mmol). Stir for 72 hours at room temperature, concentrate under reduced pressure then add ethyl acetate. Wash the ethyl acetate solution with a brine solution and dry the organic layer over  $Na_2SO_4$ . After concentrating the organic layer under reduced pressure, the reaction affords 1.93 g, 2.50 mmol (95% yield) of the title compound as a white solid:  $^1H$  NMR (500 MHz,  $CDCl_3$ ); 1.5 (9H, s), 2.75-2.85 (2H, m), 3.6-3.7 (2H, m), 4.5 (2H, s),

6.8-6.9 (2H, m), 6.9-7.0 (2H, m), 7.1-7.2 (1H, m), 7.7-7.9 (2H, m); TLC  $R_f$  = 0.5 by 2:1 hexanes:ethyl acetate eluent.

#### Intermediate 6A

##### 4-(1,2,3,4-Tetrahydro-isoquinolin-6-yloxy)-benzamide

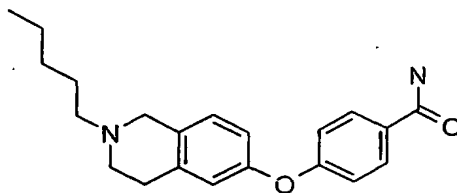


Combine 6-(4-carbamoyl-phenoxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (4.0 g, 10.83 mmol),  $\text{CH}_2\text{Cl}_2$  (100 mL), and TFA (25 mL) at room temperature. Stir for 24 hours, followed by the addition of 1.0 M  $\text{K}_2\text{CO}_3$  (aq), and extract the product out of the aqueous layer with several washings of ethyl acetate/THF.

Concentrate the organic phase under reduced pressure and add to 2, 10 g SCX Columns pre-treated with 5% AcOH/MeOH. After several washings of the SCX Columns with MeOH, elute with 1.0 N  $\text{NH}_3$ -MeOH solution to afford 2.08 g, 7.7 mmol (71% yield) of the title compound as a white foam:  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ); 2.9-3.1 (2H, m), 3.10-3.25 (1H, m), 3.3-3.5 (2H, m), 4.1-4.3 (2H, m), 7.0-7.2 (3H, m), 7.2-7.4 (1H, m), 7.4-7.6 (1H, m), 8.0-8.1 (1H, m), 8.2-8.4 (1H, m), 8.5-8.65 (1H, m), 9.2-9.4 (2H, m); MS  $m/z$  269 ( $\text{M}+1$ ).

#### Example 575

##### 4-(2-Pentyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-benzamide

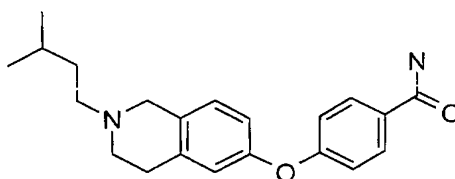


Combine 4-(1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-benzamide (80.0 mg, 0.30 mmol), DMF (4 mL),  $\text{Et}_3\text{N}$  (0.2 mL, 1.32 mmol), and pentylbromide (0.1 mL, 0.66 mmol) in a 7 mL vial. Place the vial on a shaker at 70 °C for 72 hours and then add ethyl acetate to the reaction vial. Wash with water and several times with 10% LiCl (aq), and

dry over  $\text{Na}_2\text{SO}_4$ . Concentrate the organic mixture and flash chromatograph using 2% 1.0 N  $\text{NH}_3$  in MeOH, 20% THF, 78%  $\text{CH}_2\text{Cl}_2$  to afford 78.0 mg (77% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.9-1.0 (3H, m), 1.3-1.4 (4H, m), 1.5-1.7 (2H, m), 2.4-2.6 (2H, m), 2.7-2.8 (2H, m), 2.8-3.0 (2H, m), 3.5-3.6 (2H, m), 6.8-6.8 (2H, m), 6.9-7.1 (3H, m), 7.7-7.9 (2H, m); MS  $m/z$  339 ( $\text{M}+1$ ).

#### Example 576

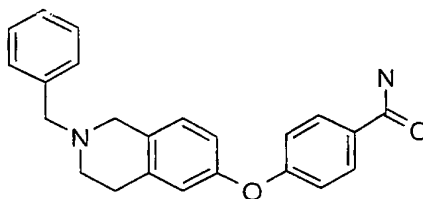
4-[2-(3-Methyl-butyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-benzamide



Using a method similar to Example 575, using isoamylbromide (0.1 mL, 0.66 mmol) gives 63.0 mg (62% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.9-1.0 (6H, m), 1.4-1.8 (3H, m), 2.5-2.6 (2H, m), 2.7-2.8 (2H, m), 2.9-3.0 (2H, m), 3.6-3.8 (2H, m), 6.8-7.1 (5H, m), 7.7-7.9 (2H, m); MS  $m/z$  339 ( $\text{M}+1$ ).

#### Example 577

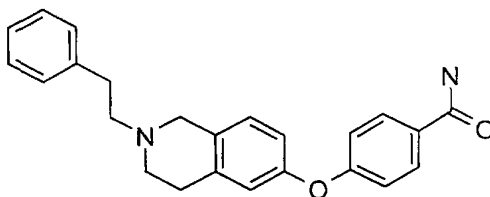
4-(2-Benzyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-benzamide



Using a method similar to Example 575, using benzylbromide (0.1 mL, 0.66 mmol) gives 81.0 mg (75% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 2.6-2.8 (2H, m), 2.8-3.0 (2H, m), 3.5-3.7 (4H, m), 5.6-6.1 (2H, br s), 6.7-6.8 (2H, m), 6.8-7.0 (3H, m), 7.2-7.4 (5H, m), 7.7-7.9 (2H, m); MS  $m/z$  359 ( $\text{M}+1$ ).

#### Example 578

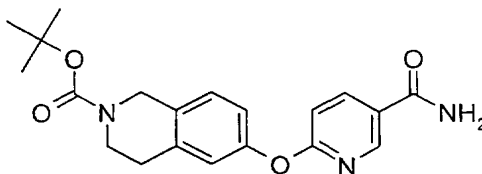
## 4-(5-Phenethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-benzamide



Using a method similar to Example 575, using intermediate 1A, and phenethylbromide (0.1 mL, 0.66 mmol) gives 81.9 mg (73% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 2.7-3.0 (7H, m), 3.6-3.8 (3H, m), 5.8-6.2 (2H, br s), 6.8-7.1 (5H, m), 7.2-7.4 (5H, m), 7.7-7.9 (2H, m); MS  $m/z$  373 ( $\text{M}+1$ ).

## Intermediate 7A

6-(5-Carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

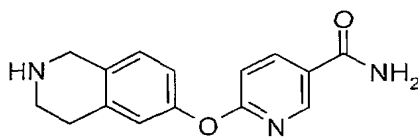


Combine in a round bottom flask equipped with a Dean Stark trap 6-hydroxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (5.42 g, 21.74 mmol), toluene, dimethylacetamide (30 mL and 90 mL respectively),  $\text{K}_2\text{CO}_3$  (4.51 g, 32.61 mmol), and 6-chloronicotinamide (3.40 g, 21.74 mmol). Reflux the reaction under a nitrogen atmosphere for 4 hours then cool to room temperature. Add water to the reaction mixture and extract the product from the water layer using ethyl acetate. The product, a white solid, precipitates out from the ethyl acetate to afford 5.8 g, 15.7 mmol (72% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ); 1.4 (9H, s), 2.7-2.9 (2H, m), 3.5-3.6 (2H, m), 4.4-4.6 (2H, m), 6.9-7.0 (2H, m), 7.0-7.1 (1H, m), 7.2-7.3 (1H, m), 7.5 (1H, s), 8.1 (1H, s), 8.2-8.3 (1H, m), 8.6 (1H, m).

## Intermediate 8A

6-(1,2,3,4-Tetrahydro-isoquinolin-6-yloxy)-nicotinamide

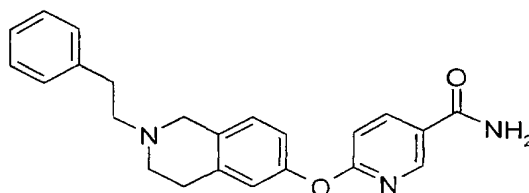
378



Combine 6-(5-carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (4.0 g, 10.83 mmol), CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and TFA (25 mL). Stir at room temperature for 12 hours and add 1.0 M K<sub>2</sub>CO<sub>3</sub> and CHCl<sub>3</sub> to the reaction. Separate the organic layer, wash with brine, and dry over Na<sub>2</sub>SO<sub>4</sub>. Concentrate under reduced pressure and add mixture to 2, 10 g SCX columns, wash with MeOH, and elute with 1.0 N NH<sub>3</sub> in MeOH. Concentrate to afford 2.91 g, 10.8 mmol (71% yield) of the title compound as a white foam: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): 2.9-3.1 (2H, m), 3.2-3.5 (2H, m), 4.2-4.4 (2H, m), 6.9-7.2 (3H, m), 7.2-7.4 (1H, m), 7.4-7.6 (1H, m), 7.9-8.1 (1H, m), 8.2-8.4 (1H, m), 8.5-8.7 (1H, m), 8.2-9.4 (2H, m); MS *m/z* 269 (M+1).

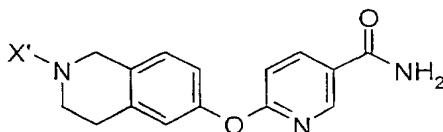
#### Example 579

6-(2-Phenethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide



Combine 6-(1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide (46.9 mg, 0.17 mmol), DMF (3 mL), Et<sub>3</sub>N (0.1 mL, 0.77 mmol), and phenethylbromide (52  $\mu$ L, 0.38 mmol) in a 7 mL vial. Place the reaction vial on a shaker at 70 °C for 72 hours, and then add water and ethyl acetate. Wash the ethyl acetate layer several times with water, 10% LiCl, and dry over Na<sub>2</sub>SO<sub>4</sub>. Concentrate organic mixture and flash chromatograph using 30% THF, 4% 1.0 N NH<sub>3</sub> in MeOH, 76% CH<sub>2</sub>Cl<sub>2</sub> to afford 23.2 mg, (37% yield) of the title compound: MS *m/z* 374(M+1).

By the method of example 579 the following compounds were prepared and isolated as the free base:



No.:	X'	Name of the Final Compound	Data
580	Benzyl	6-(2-Benzyl-1,2,3,4-tetrahydro-isoquinoline-6-yloxy)-nicotinamide	Mass spectrum (ion spray): $m/z=360$ (M+1); $^1\text{H}$ NMR (500 MHz, $\text{CDCl}_3$ ) 2.7-3.0 (4H, m), 3.6-3.8 (4H, m), 6.8-7.1 (3H, m), 7.2-7.5 (4H, m), 8.1-8.2 (1H, m), 8.5-8.7 (1H, s)
581	Pentyl	6-(2-Pentyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide	Mass spectrum (ion spray): $m/z=340$ (M+1); $^1\text{H}$ NMR (500 MHz, $\text{CDCl}_3$ ) 0.8-1.0 (3H, m), 1.2-1.4 (4H, m), 1.5-1.7 (2H, m), 2.4-2.6 (2H, m), 2.7-2.8 (2H, m), 2.8-3.0 (2H, m), 3.6-3.7 (2H, m), 5.8-6.3 (1H, br d), 6.8-7.1 (4H, m), 8.1-8.2 (1H, m), 8.5-8.7 (1H, s)
582	2-1 <i>H</i> -Indol-3-yl-ethyl	6-[2-(2-1 <i>H</i> -Indol-3-yl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=413$ (M+1);
583	2-(3-Chloro-benzyl)	6-[2-(3-Chloro-benzyl)-1,2,3,4-tetrahydro-isoquinoline-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=394$ (M+1)
584	2-(2-Carbamoyl-ethyl)	6-[2-(2-Carbamoyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=341$ (M+1);
585	2-(2-	6-[2-(2-Phenylsulfanyl-	Mass spectrum (ion spray):

	Phenylsulf anylethyl)	ethyl)-1,2,3,4-tetrahydro- isoquinolin-6-yloxy]- nicotinamide	m/z=406 (M+1);
586	2-(3-Methyl- butyl)	6-[2-(3-Methyl-butyl)- 1,2,3,4-tetrahydro- isoquinolin-6-yloxy]- nicotinamide	Mass spectrum (ion spray): m/z=340 (M+1);
587	2-(4-Trifluoro methyl- enzyl)	6-[2-(4-Trifluoromethyl- benzyl)-1,2,3,4-tetrahydro- isoquinolin-6-yloxy]- nicotinamide	Mass spectrum (ion spray): m/z=428 (M+1);
588	2-(3-Chloro- benzyl)	6-[2-(3-Chloro-benzyl)- 1,2,3,4-tetrahydro- isoquinolin-6-yloxy]- nicotinamide	Mass spectrum (ion spray): m/z=394 (M+1);
589	2-(3-Phenyl- allyl)	6-[2-(3-Phenyl-allyl)- 1,2,3,4-tetrahydro- isoquinolin-6-yloxy]- nicotinamide	Mass spectrum (ion spray): m/z=386 (M+1);
590	2-(5-Chloro- benzo[b]th iophen-3- ylmethyl	6-[2-(5-Chloro- benzo[b]thiophen-3- ylmethyl-1,2,3,4- tetrahydro-isoquinolin-6- yloxy)-nicotinamide	Mass spectrum (ion spray): m/z=450 (M+1)
591	2-Cycloprop ylmethyl	6-(2-Cyclopropylmethyl- 1,2,3,4-tetrahydro- isoquinolin-6-yloxy)- nicotinamide	Mass spectrum (ion spray): m/z=324 (M+1);
592	2-(3,5-Bis- trifluorom	6-[2-(3,5-Bis- trifluoromethyl-benzyl)- 1,2,3,4-tetrahydro-	Mass spectrum (ion spray): m/z=496 (M+1);



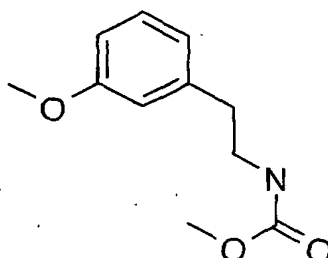
	ethyl-benzyl)	isoquinolin-6-yloxy]-nicotinamide	
593	2-(3-Bromo-benzyl)	6-[2-(Bromo-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=438$ (M);
594	2-(4-Methyl-benzyl)	6-[2-(4-Methyl-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=374$ (M+1);
595	2-(2-Fluoro-benzyl)	6-[2-(2-Fluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=378$ (M+1);
596	2-(3-Methoxy-benzyl)	6-[2-(3-Methoxy-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=390$ (M+1);
597	2-(1 <i>H</i> -Benzoimidazol-2-ylmethyl)	6-[2-(1 <i>H</i> -Benzoimidazol-2-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=400$ (M+1);
598	2-(5-Chloro-thiophen-2-ylmethyl)	6-[2-(5-Chloro-thiophen-2-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=400$ (M+1);
599	2-(2,6-Dichloro-benzyl)	6-[2-(2,6-Dichloro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=428$ (M);

600	2-(3-Fluoro-benzyl)	6-[2-(3-Fluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=378$ (M+1);
601	2-[2-(4-Methoxy-phenyl)-ethyl]	6-{2-[2-(4-Methoxy-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinolin-6-yloxy}-nicotinamide	Mass spectrum (ion spray): $m/z=404$ (M+1);
602	3-Propionic acid	3-[6-(5-Carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1 <i>H</i> -isoquinolin-2yl]-propionic acid	Mass spectrum (ion spray): $m/z=342$ (M+1);
603	2-(3-Piperidin-1-yl-propyl)	6-[2-(3-Piperidin-1-yl-propyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=395$ (M+1);
604	2-Pent-4-ynyl	6-(2-Pent-4-ynyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide	Mass spectrum (ion spray): $m/z=336$ (M+1);
605	2-(2-Piperidin-1-yl-ethyl)	6-[2-(2-Piperidin-1-yl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=381$ (M+1);
606	2-(2-Diisopropylamino-ethyl)	6-[2-(2-Diisopropylamino-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=397$ (M+1);
607	2-(3,3,4,4-Tetrafluoro-butyl)	6-[2-(3,3,4,4-Tetrafluoro-butyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): $m/z=398$ (M+1);

608	2-Cyclobutylmethyl	6-(2-Cyclobutylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide	Mass spectrum (ion spray): m/z=338 (M+1);
609	2-(3,3-Dimethyl-butyl)	6-[2-(3,3-Dimethyl-butyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): m/z=354 (M+1);
610	2-(3,4,4-Trifluoro-but-3-enyl)	6-[2-(3,4,4-Trifluoro-but-3-enyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): m/z=378 (M+1);
611	2-(2-Methoxy-benzyl)	6-[2-(2-Methoxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): m/z=390 (M+1);
612	2-Pyridin-3-ylmethyl	6-(2-Pyridin-3-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide	Mass spectrum (ion spray): m/z=361 (M+1);

## Intermediate 9A

[2-(3-Methoxy-phenyl)-ethyl]-carbamic acid methyl ester

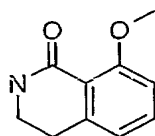


Combine 2-(3-methoxyphenyl)ethylamine (9.6 mL, 66.1 mmol), THF (300 mL), Et<sub>3</sub>N (11.0 mL, 78.9 mmol), and methyl chloroformate (26.0 mL, 339 mmol) at 0 °C under nitrogen atmosphere. Stir at room temperature for 18 hours, add the mixture into

water, wash with brine, and dry the organic layer over  $\text{Na}_2\text{SO}_4$  followed by concentrating under reduced pressure. Flash chromatograph using 2:1 hexanes:ethyl acetate to afford 13.6 g, 65.0 mmol (98% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 2.8 (2H, t,  $J = 6.7, 7.0$  Hz), 3.41-3.46 (2H, m), 3.7 (3H, s), 3.8 (3H, s), 4.6-4.8 (1H, br s), 6.7-6.8 (3H, m), 7.2-7.3 (1H, m); MS  $m/z$  210 ( $M+1$ ).

#### Intermediate 10A

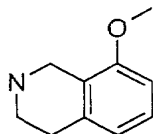
##### 8-Methoxy-3,4-dihydro-2H-isoquinolin-1-one



Combine polyphosphoric acid (30 g) at 180 °C and [2-(3-methoxy-phenyl)-ethyl]-carbamic acid methyl ester (3.0 g, 14.33 mmol). Stir for 15 minutes then add to a beaker of ice. Extract the product from the water using  $\text{CH}_2\text{Cl}_2$  and  $\text{CHCl}_3$ . Dry the organic layer over  $\text{Na}_2\text{SO}_4$  and then concentrate under reduced pressure. Flash chromatograph using 5% MeOH in ethyl acetate to afford 0.340 g, 1.92 mmol (13% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 2.92 (2H, t,  $J = 6.4$  Hz), 3.43-3.47 (2H, m), 3.85 (3H, s), 6.2-6.3 (1H, br s), 6.8-6.9 (2H, m), 7.3-7.4 (1H, m), 7.5-7.6 (2H, m); MS  $m/z$  178 ( $M+1$ ).

#### Intermediate 11A

##### 8-Methoxy-1,2,3,4-tetrahydro-isoquinoline

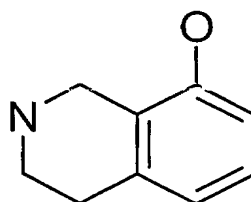


Combine 8-methoxy-3,4-dihydro-2H-isoquinolin-1-one (0.778 g, 4.40 mmol), THF (20 mL), and  $\text{LiAlH}_4$  (0.333 g, 8.8 mmol) at 0 °C under nitrogen atmosphere. After 30 minutes of the reaction, reflux for 2 hours and then cool to room temperature. Quench the reaction by adding water and 1.0 M NaOH at 0 °C and stirring for 12 hours at room temperature. Filter the reaction through Celite® and elute with THF. After concentrating the filtrate under reduced pressure, add the mixture to a 10 g SCX column pre-treated

with 5% AcOH/MeOH. After rinsing several times with MeOH, elute the product using 1.0 N  $\text{NH}_3$ -MeOH followed by concentration under reduced pressure to afford 0.665 g, 4.07 mmol (93% yield) of the title compound as a tan oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.7-2.0 (1H, b s), 2.77 (2H, t,  $J=5.86$  Hz), 3.09 (2H, t,  $J=5.86$  Hz), 3.8 (3H, s), 3.95 (2H, s), 6.6-6.8 (2H, m), 7.0-7.15 (1H, m); TLC 5% MeOH:ethyl acetate  $R_f=0.1$

#### Intermediate 12A

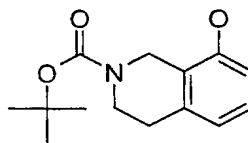
##### 1,2,3,4-Tetrahydro-isoquinolin-8-ol



Combine 8-methoxy-tetrahydroisoquinoline (665.7 mg, 4.08 mmol) and 48% HBr at room temperature. Reflux the reaction for 3 hours and then cool to room temperature. Recrystallize the product from EtOH and diethyl ether to afford 754.2 mg, 3.28 mmol (80% yield) of the title compound as a tannish white solid:  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ); 2.9 (2H, t,  $J=6.16, 5.86$  Hz), 3.2-3.4 (2H, m), 4.0 (2H, s), 6.6-6.8 (2H, m), 7.0-7.1 (1H, m), 8.8-9.1 (2H, br m), 9.9 (1H, s); MS  $m/z$  148 (M-1).

#### Intermediate 13A

##### 8-Hydroxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

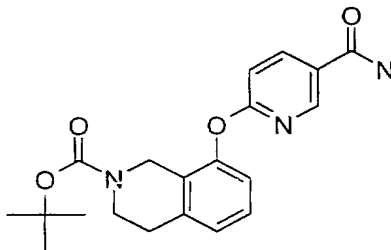


Combine 8-hydroxy tetrahydroisoquinoline HBr salt (754.2 mg, 3.28 mmol), and  $\text{Et}_3\text{N}$  (2.8 mL, 19.68 mmol), anhydrous THF (20 mL), and BOC-anhydride (1.14g, 3.94 mmol). Stir the reaction at room temperature for 72 hours followed by an aqueous work-up. Wash the organic layer with brine and dry over  $\text{Na}_2\text{SO}_4$ . After concentrating the organic layer under reduced pressure, flash chromatograph using 4:1 hexanes:ethyl acetate eluent to afford 249.6 mg, 1.01 mmol (31% yield) of the title compound as a white foam:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.5 (9H, s), 2.73-2.79 (2H, m), 3.5-3.6 (2H,

m), 4.45-4.61 (2H, b s), 6.6-6.9 (2H, m), 6.9-7.2 (1H, m); TLC 4:1 hexanes:ethyl acetate  $R_f$ =0.13

#### Intermediate 14A

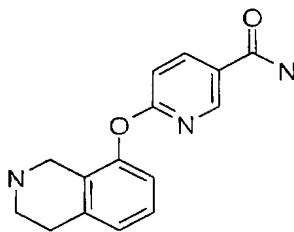
8-(5-Carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester



Combine in a 100 mL round bottom flask equipped with a stir bar, a Dean Stark trap, and a reflux condenser 8-hydroxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (249.6 mg, 1.01 mmol), dimethylacetamide (30 mL), toluene (10 mL),  $K_2CO_3$  (814.74 mg, 5.90 mmol), and 6-chloronicotinamide (626.28 mg, 4.0 mmol). Reflux the reaction under nitrogen for 5 hours. After cooling to room temperature, add water to the reaction mixture and extract the product using ethyl acetate. Wash the organic layer with brine and dry over  $Na_2SO_4$ . After concentrating under reduced pressure, flash chromatograph using 20% THF in  $CH_2Cl_2$  to afford 245.1mg, 0.66 mmol (66% yield) of the title compound:  $^1H$  NMR (500 MHz,  $CD_3OD$ ); 1.3-1.5 (9H, m), 2.8-2.9 (2H, m), 3.5-3.7 (2H, m), 3.85 (2H, s), 6.9-7.0 (1H, m), 7.1-7.2 (1H, m), 7.2-7.3 (1H, m), 7.5-7.6 (1H, m), 8.2-8.3 (1H, m), 8.6-8.7 (1H, br s), 8.8 (1H, s); MS  $m/z$  370 (M+1).

#### Intermediate 15A

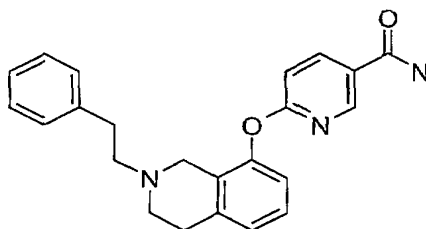
6-(1,2,3,4-Tetrahydro-isoquinolin-8-yloxy)-nicotinamide



Combine 8-(5-carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (249.6 mg, 1.01 mmol), CH<sub>2</sub>Cl<sub>2</sub> (25 mL), and TFA (10 mL) at room temperature under nitrogen atmosphere. Stir for 12 hours then concentrate under reduced pressure. Solubilize the mixture in MeOH and add to a 2 g SCX Column (pre-treated with 5% AcOH-MeOH), wash several times with MeOH, and elute with 1.0 N NH<sub>3</sub> in MeOH to afford 156.1 mg, 0.58 mmol (57% yield) of the title compound.

### Example 613

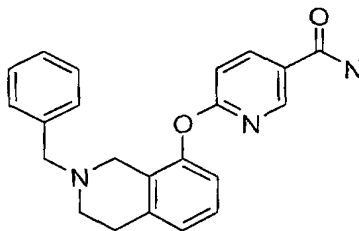
6-(2-Phenethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-nicotinamide



Using a method similar to Example 24, using phenethylbromide (40  $\mu$ L, 0.28 mmol) gives 26.9 mg (55% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.8-2.1 (4H, m), 2.7-3.0 (6H, m), 5.9-6.3 (2H, br d), 6.8-7.4 (10H, m), 8.1-8.3 (1H, m), 8.5 (1H, s); MS *m/z* 374 (M+1).

### Example 614

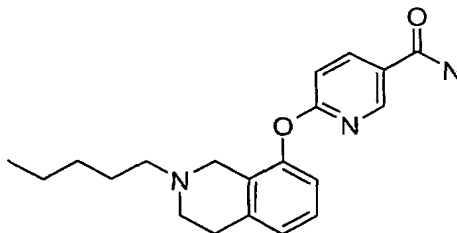
6-(2-Benzyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-nicotinamide



Using a method similar to Example 24, using benzylbromide (0.1 mL, 0.97 mmol) gives 45.6 mg (63% yield) of the title compound.

**Example 615**

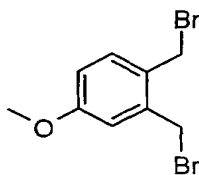
6-(2-Pentyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-nicotinamide



Using a method similar to Example 24, using pentylbromide (54  $\mu$ L, 0.48 mmol) gives 32.5 mg (48% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ); 0.8 (3H, t), 1.2-1.3 (4H, m), 1.4-1.6 (2H, m), 2.3-2.5 (2H, m), 2.7 (2H, t), 2.9-3.0 (2H, m), 3.5 (2H, s), 6.8-7.2 (5H, m), 8.1-8.2 (1H, m), 8.6 (1H, s); MS  $m/z$  340 ( $M+1$ ).

**Intermediate 16A**

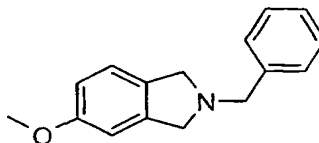
1,2-Bis-bromomethyl-4-methoxy-benzene



Combine 3,4-dimethylanisole (2.72 g, 20.0 mmol),  $\text{CCl}_4$  (50 mL), NBS (7.12 g, 40.0 mmol), and benzoyl peroxide (40.0 mg, 0.17 mmol). Reflux the reaction for 12 hours and then cool to room temperature and concentrate under reduced pressure. Flash chromatograph using 4:1  $\text{CHCl}_3$ :hexanes eluent to afford 1.90g, 6.4 mmol (32% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 3.8 (3H, s), 4.6 (2H, s), 4.7 (2H, s), 6.8-6.9 (2H, m), 7.1-7.4 (1H, m); TLC 4:1  $\text{CHCl}_3$ :hexanes  $R_f$ =0.67

**Intermediate 17A**

2-Benzyl-5-methoxy-2,3-dihydro-1H-isoindol

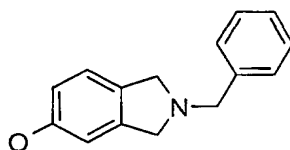




Combine in a round bottom flask 1,2-bis-bromomethyl-4-methoxy-benzene (1.0 g, 3.40 mmol), benzyltriethylammonium chloride (73.5 mg, 3.2 mmol), 50% NaOH (aq) / toluene (3.0 mL / 14 mL), and then drop wise add benzylamine (0.37mL, 3.39 mmol). Stir the reaction at room temperature for 3 hours, add to ethyl acetate, wash with water, brine, and dry over Na<sub>2</sub>SO<sub>4</sub>. After concentrating under reduced pressure, add the mixture to a 10 g SCX column, wash with MeOH, and elute with 1.0 N NH<sub>3</sub>-MeOH. Flash chromatograph using 3:1 hexanes:ethyl acetate to afford 580.0 mg, 2.42mmol (71% yield) of the title compound as a brown oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 3.7 (3H, s), 3.9-4.0 (6H, m), 6.7-6.8 (2H, m), 7.1 (1H, d), 7.3-7.5 (5H, m); MS *m/z* 238 (M-1).

#### Intermediate 18A

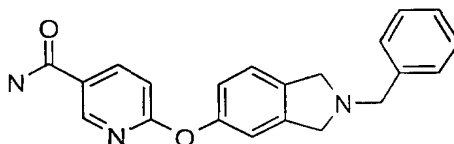
##### 2-Benzyl-2,3-dihydro-1*H*-isoindol-5-ol



Combine 2-benzyl-5-methoxy-2,3-dihydro-1*H*-isoindol (580.0 mg, 2.42 mmol) and 48% HBr (aq) (20 mL). Reflux the reaction for 5 hours and then cool to room temperature. Concentrate the reaction mixture under reduced pressure then add to 5 g SCX column. Wash the column with MeOH and elute with 1.0 N NH<sub>3</sub>-MeOH to afford 265.4 mg, 1.17 mmol (49% yield) of the title compound as a brown solid: <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD); 3.8-3.9 (4H, m), 3.91 (2H, s), 6.6-6.7 (2H, m), 7.0 (1H, d), 7.2-7.5 (5H, m); MS *m/z* 226 (M+1).

#### Example 616

##### 6-(2-Benzyl-2,3-dihydro-1*H*-isoindol-5-yloxy)-nicotinamide

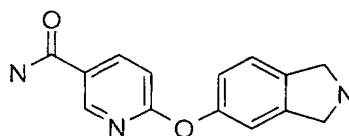


Combine in a round bottom flask equipped with a stir bar and a Dean Stark trap under a nitrogen atmosphere 2-benzyl-2,3-dihydro-1*H*-isoindol-5-ol (265.4 mg, 1.18 mmol), toluene (10 mL), DMA (30 mL), K<sub>2</sub>CO<sub>3</sub> (244.6 mg, 1.77 mmol), and 6-

chloronicotinamide (184.4 mg, 1.18 mmol). Reflux the reaction for 6 hours and then cool to room temperature. Add ethyl acetate, wash the ethyl acetate layer several times with water, brine, and dry over Na<sub>2</sub>SO<sub>4</sub>. After concentrating under reduced pressure, purify the mixture by reverse phase chromatography (5% to 95% (0.01% TFA buffer in acetonitrile)/water) to afford 333.4 mg, 0.97 mmol (82% yield) of the title compound as a white foam: <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD); 4.6-4.8 (6H, m), 7.0 (1H, d), 7.1-7.2 (2H, m), 7.4-7.6 (6H, m), 8.2 (1H, d), 8.6 (1H, s); MS *m/z* 346 (M+1).

#### Intermediate 19A

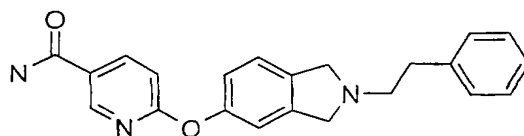
6-(2,3-Dihydro-1*H*-isoindol-5-yloxy)-nicotinamide



Combine 6-(2-benzyl-2,3-dihydro-1*H*-isoindol-5-yloxy)-nicotinamide (230.0 mg, 0.67 mmol), EtOH (5 mL), and 10% Pd-C (45.0 mg) and place under a hydrogen balloon. Stir the reaction at room temperature for 168 hours at atmospheric pressure. Filter the reaction mixture through a pad of Celite® using MeOH eluent and then concentrate the filtrate under reduced pressure. Add the mixture to a 2 g SCX column, wash with MeOH, and elute using 1.0 N NH<sub>3</sub>-MeOH. After concentrating under reduced pressure, purify the mixture by flash chromatography using 10% 1.0 N NH<sub>3</sub>-MeOH/DCM eluent to afford 19.2 mg, 0.08 mmol (11% yield) of the title compound as a white solid: <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD); 4.1-4.3 (4H, br m), 6.9-7.1 (3H, m), 7.3-7.4 (1H, m), 8.2-8.3 (1H, m), 8.6 (1H, s); MS *m/z* 254 (M-1).

#### Example 617

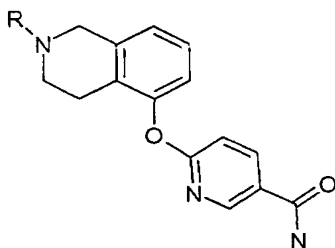
6-(2-Phenethyl-2,3-dihydro-1*H*-isoindol-5-yloxy)-nicotinamide



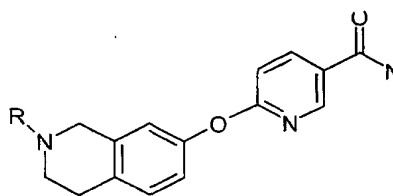
Combine 6-(2,3-dihydro-1*H*-isoindol-5-yloxy)-nicotinamide (19.2 mg, 0.08 mmol), DMF (3 mL), Et<sub>3</sub>N (46 uL, 0.33 mmol), and 2-phenethylbromide (23 uL, 0.165

mmol). Place the reaction on a shaker for 12 hours at 70 °C, then cool to room temperature and concentrate under reduced pressure. Add the mixture to a 2 g SCX column, wash with MeOH, and then elute with 1.0 N NH<sub>3</sub>-MeOH. After concentrating the mixture, purify using reverse phase chromatography (5% to 95% (0.001% TFA buffer in acetonitrile)/water) to afford 9.5 mg, 0.03 mmol (33% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD); 2.8-3.2 (4H, m), 4.1-4.2 (4H, m), 6.8-7.1 (3H, m), 7.2-7.4 (6H, m), 8.2 (1H, d), 8.6 (1H, s); MS *m/z* 358 (M-1).

### Examples 618-636



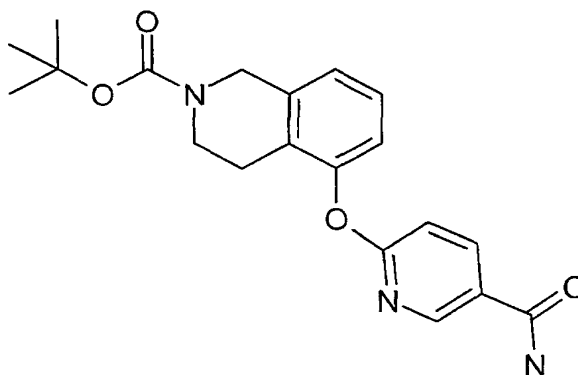
Examples 618-625



Examples 626-639

### Example 618

5-(5-Carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

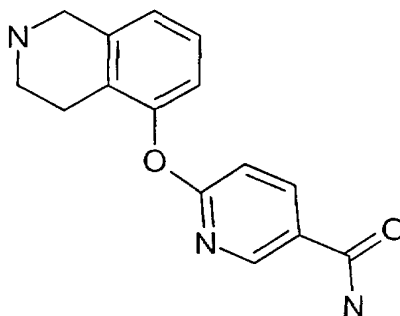


Combine 5-hydroxy, 3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (2.0g, 8mmol), cesium carbonate (5.2 g, 16 mmol) and *N,N*-dimethylformamide (60 mL), stir at room temperature for 30 minutes. Add 6-chloronicotinamide (1.2 g, 8 mmol)

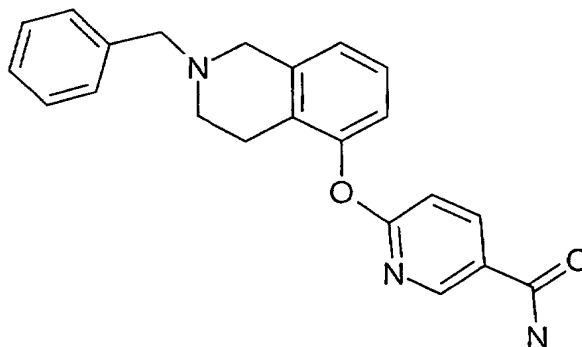
and heat at 100 °C for 2 days. Cool to room temperature, dilute with brine, and then extract with ethyl acetate (3 x 150 mL). Dry the ethyl acetate extracts with sodium chloride/magnesium sulfate, filter, then concentrate on a rotary evaporator to yield 3 g of the crude product. The crude product is purified by flash column chromatography on silica gel eluting with 0.5% conc. ammonium hydroxide / 5% ethanol in chloroform to yield 5-(5-carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (2.1 g, 5.7 mmol): <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300.00 MHz): 8.54 (s, 1H); 8.30-8.23 (m, 1H); 8.02-7.93 (m, 1H); 7.48 (s, 1H); 7.23 (d, 1H); 7.09-6.95 (m, 1H); 4.54 (s, 2H); 3.48-3.36 (m, 4H); 2.87-2.71 (m, 2H); 1.39 (s, 9H).

### Example 619

6-(1,2,3,4-Tetrahydro-isoquinolin-5-yloxy)-nicotinamide



Add drop wise via an addition funnel a solution of trifluoroacetic acid (5.7 mL) in dichloromethane (25 mL) to a stirred solution of 5-(5-carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (2.1 g, 5.7 mmol) in dichloromethane (75 mL) at 0°C. Warm to room temperature and stir for 18 hours. Evaporate on a rotary evaporator, dissolve the residue in methanol (50 mL) and dichloromethane (50 mL), and then add MP-carbonate resin (7.9 g @ 2.87 eq/g). Agitate for 2 hours, filter, concentrate on a rotary evaporator, and dry under vacuum to yield 6-(1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-nicotinamide (1.5 g, 5.6 mmol): HPLC = 85% (50/50 to 90/10 ACN/(0.1%TFA in water), Zorbax SB-Phenyl 4.6 mm x 15 cm x 5 micron, λ = 254nm). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300.00 MHz): 8.55 (d, 1H), 8.23 (dd, 1H), 8.01 (s, 1H), 7.46 (s, 1H), 6.95 (m, 5H), 3.90 (s, 2H), 2.85 (m, 2H), 2.38 (m, 2H),.

**Example 620****6-(2-Benzyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-nicotinamide**

Combine 6-(1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-nicotinamide (100 mg, 0.37 mmol), benzaldehyde (39  $\mu$ L, 0.38 mmol), sodium triacetoxyborohydride (101 mg, 0.48 mmol), acetic acid (22  $\mu$ L, 0.39 mmol), and 1,2-dichloroethane (5 mL) then stir at room temperature for 18 hours. Dilute the reaction with saturated aqueous sodium bicarbonate solution and extract with dichloromethane (3 x 25 mL). Dry the combined dichloromethane extracts with sodium chloride/magnesium sulfate, filter, and concentrate on a rotary evaporator to yield 45 mg of the crude product. The crude product is purified by flash column chromatography on silica gel eluting with (0.5% conc. ammonium hydroxide / 5% ethanol) to (1% conc. ammonium hydroxide / 10% ethanol) in chloroform to yield 6-(2-benzyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-nicotinamide (31 mg, 0.09 mmol):  $m/z$  = 360.1(M+1);  $^1\text{H}$  NMR (DMSO- $d_6$ , 300.00 MHz): 8.56 (s, 1H); 8.16-8.12 (m, 1H); 7.38-7.15 (m, 6H); 6.94-6.89 (m, 3H); 6.17 (s, 2H); 3.74-3.61 (m, 4H); 2.69-2.66 (m, 4H), HPLC = 99% (30/70 to 90/10 ACN/(0.1%TFA in water), Zorbax SB-Phenyl 4.6 mm x 15 cm x 5 micron,  $\lambda$  = 254 nm).

By the method of Example 620 the following compounds were prepared and isolated as the free base except where noted:

Example	Name	Data
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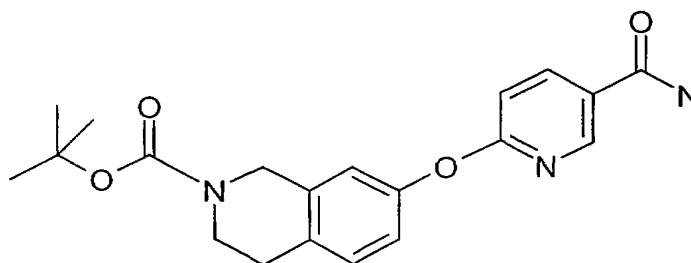
		Mass spectrum (ion spray): m/z (M+1)	HPLC (30/70 to 90/10 ACN/(0.1% TFA in water), Zorbax SB- Phenyl 4.6 mm x 15 cm x 5 micron, $\lambda$ = 254 nm)	
			Purity	Retention Time (minutes)
621	6-(2-Butyl-1,2,3,4- tetrahydro-isoquinolin-5- yloxy)-nicotinamide	326.16	96	2.55
622	6-[2-(3-Methyl-butyl)- 1,2,3,4-tetrahydro- isoquinolin-5-yloxy]- nicotinamide	340.17	99	3.16
623	6-(2-Thiophen-2- ylmethyl-1,2,3,4- tetrahydro-isoquinolin-5- yloxy)-nicotinamide	366.07	99	2.57
624	6-(2-Phenethyl-1,2,3,4- tetrahydro-isoquinolin-5- yloxy)-nicotinamide	374.14	100	4.19
625	6-(2-Hexyl-1,2,3,4- tetrahydro-isoquinolin-5- yloxy)-nicotinamide	354.2	94	
626	6-(2-Isopropyl-1,2,3,4- tetrahydro-isoquinolin-5- yloxy)-nicotinamide	312.13	60	
627	6-(2-Propyl-1,2,3,4- tetrahydro-isoquinolin-5-	312.15	71	1.94

	yloxy)-nicotinamide			
628	6-(2-Isobutyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-nicotinamide	326.15	98	2.15
629	6-(2-Pentyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-nicotinamide	340.17	99	3.20
630	6-(2-Furan-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-nicotinamide	350.11	98	2.17
631	6-(2-Cyclohexyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-nicotinamide	352.16	96	2.76
632	6-(2-Pyridin-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-nicotinamide	361.13	76	1.95
633	6-(2-Pyridin-3-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-nicotinamide	361.13	99	1.53
634	6-(2-Pyridin-4-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-nicotinamide	361.13	99	1.57
635	6-(2-Cyclohexylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-nicotinamide	366.18	94	4.19

636	6-[2-(3-Phenyl-propyl)- 1,2,3,4-tetrahydro- isoquinolin-5-yloxy]- nicotinamide	388.16	94	5.60
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**Example 637**

7-(5-Carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester



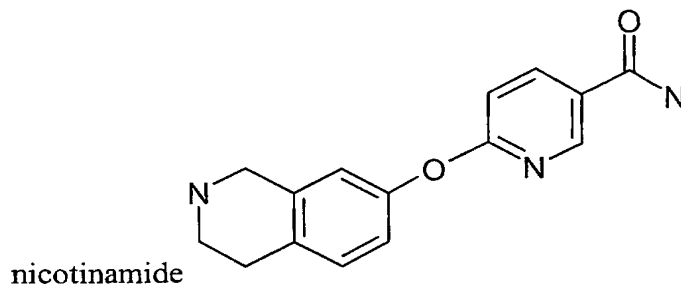
Combine 7-hydroxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (1.7 g, 6.8 mmol, Reference *J. Med. Chem.* **1998**, *41* (25), 4983-4994), cesium carbonate (4.4 g, 13.6 mmol) and *N,N*-dimethylformamide (75 mL) and stir at room temperature for 30 minutes. Add 6-chloronicotinamide (1.1 g, 6.8 mmol) and heat at 100 °C for 2 days. Cool to room temperature, dilute with brine then extract with ethyl acetate (3 x 125 mL). Dry the ethyl acetate extracts with sodium chloride/magnesium sulfate, filter, then concentrate on a rotary evaporator to yield 12 g of the crude product. The crude product is purified by flash column chromatography on silica gel eluting with (0.1% conc. ammonium hydroxide / 1% ethanol) to (1% conc. ammonium hydroxide / 10% ethanol) in chloroform to yield 7-(5-carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (1.2 g, 3.3 mmol): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300.00 MHz): 8.59 (s, 1H); 8.17 (d, 1H); 7.20-7.17 (m, 2H); 6.98-6.89 (m, 2H); 5.97 (s, 2H); 4.57 (s, 2H); 3.68-3.66 (m, 2H); 2.83 (t, 2H); 1.48 (s, 9H).

**Example 638**



397

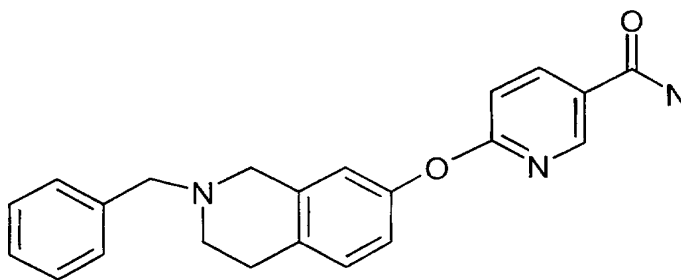
6-(1,2,3,4-Tetrahydro-isoquinolin-7-yloxy)-



Add drop wise via an addition funnel a solution of trifluoroacetic acid (3.3 mL) in dichloromethane (10 mL) to a stirred solution of 7-(5-carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (1.2 g, 3.3 mmol) in dichloromethane (50 mL) at 0 °C. Warm to room temperature and stir for 18 hours. Evaporate on a rotary evaporator, dissolve the residue in methanol, and then apply in equal parts to 2-10 g SCX cartridges. Wash each cartridge with methanol until neutral pH then elute product with 2.0 M ammonia in methanol. Collect the basic eluent and concentrate on a rotary evaporator to yield 6-(1,2,3,4-tetrahydro-isoquinolin-7-yloxy)-nicotinamide (0.9 g, 3.3 mmol): <sup>1</sup>H NMR(CDCl<sub>3</sub>, 300.00 MHz): 8.57 (s, 1H); 8.15 (d, 1H); 7.15-7.13 (m, 1H); 6.96-6.89 (m, 2H); 6.80 (s, 1H); 5.87 (br, 2H); 4.01 (s, 2H); 3.17-3.13 (m, 2H); 2.82-2.78 (m, 2H); 1.73 (br, 1H).

### Example 639

6-(2-Benzyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy)-nicotinamide



Combine 6-(1,2,3,4-tetrahydro-isoquinolin-7-yloxy)-nicotinamide (94 mg, 0.35 mmol), benzaldehyde (37  $\mu$ L, 0.37 mmol), sodium triacetoxyborohydride (96 mg, 0.46 mmol), acetic acid (21  $\mu$ L, 0.37 mmol), and 1,2-dichloroethane (5 mL) then stir at room

temperature for 18 hours. Dilute the reaction with saturated aqueous sodium bicarbonate solution and extract with 5% methanol in dichloromethane (3 x 25 mL). Dry the combined 5% methanol in dichloromethane extracts with sodium chloride/magnesium sulfate, filter, and concentrate on a rotary evaporator to yield 100 mg of the crude product. The crude product is purified by flash column chromatography on silica gel eluting with 1% conc. ammonium hydroxide / 10% ethanol in chloroform to yield 6-(2-benzyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy)-nicotinamide 2039910 (30 mg, 0.09 mmol):  $m/z = 360.12(M+1)$ ;  $^1H$  NMR ( $CDCl_3$ , 300.00 MHz): 8.50 (d, 1H); 8.09-8.05 (m, 1H); 7.34-7.20 (m, 5H); 7.09 (d, 1H); 6.87-6.82 (m, 2H); 6.71 (d, 1H); 5.80 (s, 2H); 3.63-3.57 (m, 4H); 2.87-2.69 (m, 4H), HPLC = 96% @ 2.98 m (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6 mm x 15 cm x 5 micron,  $\lambda = 254$  nm).

By the method of Example 639 the following compounds were prepared and isolated as the free base except where noted:

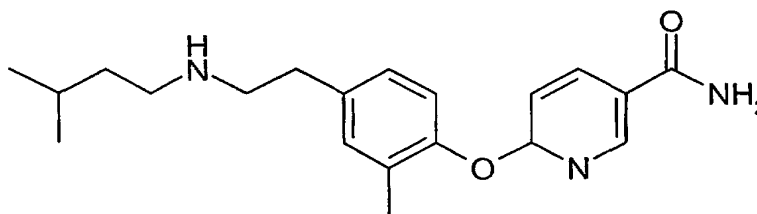
Example	Name	Data		
		Mass spectrum (ion spray): $m/z$ (M+1)	HPLC (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6 mm x 15 cm x 5 micron, $\lambda = 254$ nm)	
			Purity	Retention Time (minutes)
640	6-(2-Propyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy)-nicotinamide	312.1	94	6.08

641	6-(2-Cyclohexyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy)-nicotinamide	352.1	96	6.32
642	6-[2-(3-Cyclohexyl-propyl)-1,2,3,4-tetrahydro-isoquinolin-7-yloxy]-nicotinamide	394.2	90	6.84
643	6-(2-Pentyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy)-nicotinamide	340.1	96	6.38
644	6-(2-Cyclohexylmethyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy)-nicotinamide	366.1	98	6.45
645	6-(2-Phenethyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy)-nicotinamide	374.1	96	6.46
646	6-[2-(3-Phenyl-propyl)-1,2,3,4-tetrahydro-isoquinolin-7-yloxy]-nicotinamide	388.1	99	6.53
647	6-(2-Pyridin-3-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy)-nicotinamide	361.1	99	5.8
648	6-(2-Thiophen-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy)-nicotinamide	366	99	6.24

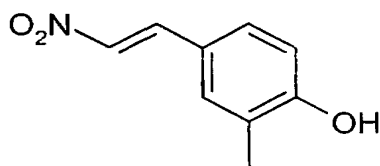
649	6-(2-Furan-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-7-yloxy)-nicotinamide	350.1	96	6.14
650	6-[2-(3-Chloro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-7-yloxy]-nicotinamide	394	98	6.47

**Example 651**

6-{2-Methyl-4-[2-(3-methyl-butylamino)-ethyl]-phenoxy}-nicotinamide

**Step 1**

2-Methyl-4-(2-nitro-vinyl)-phenol

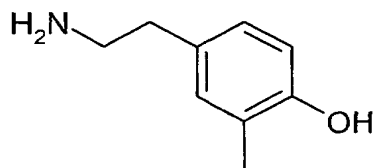


The 2-methyl-4-hydroxy-benzaldehyde (980 mg, 6.3 mmol), nitromethane (2.0 mL, 37.7 mmol) and ammonium acetate (1.9 g, 25.1 mmol) were dissolved in acetic acid (9 mL) and the reaction heated at 110°C for 2 h. The reaction is concentrated under reduced pressure and the residue partitioned between ether and water. Separate the layers and dry with Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate under reduced pressure. Purify the crude by flash chromatography (eluent: EtOAc/hexane 20/80 and 30/70) afforded the title compound (1.0 g). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): 7.94 (d, 1H, J= 13.4 Hz), 7.50 (d, 1H, J= 13.6 Hz), 7.34-7.27 (m, 2H), 6.82 (d, 1H, J= 8.1 Hz), 2.28 (s, 3H).

401

## Step 2

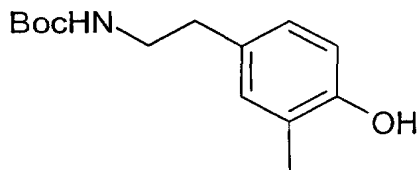
## 4-(2-Amino-ethyl)-2-methyl-phenol



Procedure 1: Dissolve compound obtained in step 1 above (440 mg, 2.46 mmol) in methanol (10 mL) and add Pd/C 10% (272 mg) and HCl conc (1 mL). Stir the mixture at room temperature under hydrogen overnight. Filtrate over celite and eliminate the solvent. Purify by SCX column to obtain the title compound (232 mg, 63%).

Procedure 2: To lithium aluminum hydride 1.0M in ether (1.67 mL, 1.67 mmol) at 0°C a solution of aluminum trichloride (224 mg, 1.67 mmol) in THF (2 mL) is added. After 5 min a solution of compound obtained in step 1 above (100 mg, 0.56 mmol) in THF (2 mL) is added and the reaction is allowed to stir at room temperature overnight. Add water and then 3 N HCl, the aqueous layer is extracted with 3/1 n-butanol/toluene. The combined organic layers are dried over sodium sulfate and concentrated. SCX ion-exchange chromatography afforded 71 mg (84%) of the title compound. Electrospray MS M+1 ion= 152. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 6.89 (bs, 1H), 6.82 (dd, 1H, J= 8.3 and 2.4 Hz), 6.64 (d, 1H, J= 8.1 Hz), 2.80 (t, 2H, J= 6.7 Hz), 2.61 (t, 2H, J= 7.0 Hz), 2.15 (s, 3H).

## Step3

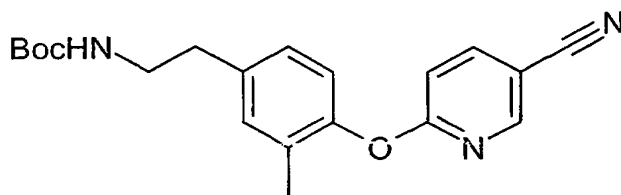
[2-(4-Hydroxy-3-methyl-phenyl)-ethyl]-carbamic acid *tert*-butyl ester

Dissolve amine obtained in step 2 above (289 mg, 1.91 mmol) in dry THF (5 mL) under N<sub>2</sub> atmosphere, add a solution of di-*tert*butyl dicarbonate (439 mg, 2.0 mmol) in THF (5 mL), stir the mixture at room temperature overnight. Eliminate the solvent to obtain the

title compound (462 mg, 96%). TLC  $R_f$  (EtOAc/hexane 20/80): 0.27.  $^1\text{H-NMR}$  (methanol- $d_4$ , 200 MHz): 6.88 (bs, 1H), 6.82 (d, 1H,  $J = 8.3$  Hz), 6.63 (d, 1H,  $J = 8.1$  Hz), 3.17 (t, 2H,  $J = 6.7$  Hz), 2.60 (t, 2H,  $J = 7.0$  Hz), 2.14 (s, 3H), 1.50 (s, 9H).

#### Step 4

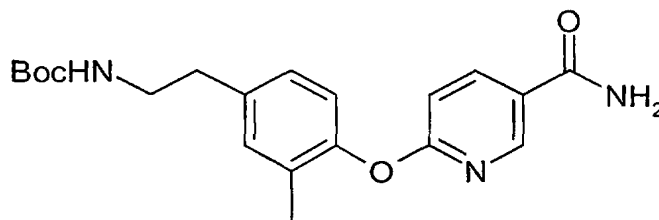
{2-[4-(5-Cyano-pyridin-2-yloxy)-3-methyl-phenyl]-ethyl}-carbamic acid *tert*-butyl ester



A solution of phenol obtained in step 3 above (455 mg, 1.1 mmol), 6-chloronicotinonitrile (251 mg, 1.81 mmol) and sodium hydride (87 mg, 2.17 mmol) in DMSO (10 mL) is stirred at room temperature for 18 h. Pour the mixture into iced water and extract the aqueous layer with EtOAc. Dry the organic layer over  $\text{Na}_2\text{SO}_4$ , filtrate and eliminate the solvent. Purify by flash chromatography (eluent: EtOAc/hexane 15/85 and 20/80) to get the title compound (358 mg, 57%). Electrospray MS  $M^+ + 1$ -Boc group ion: 298.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz): 8.42 (dd, 1H,  $J = 0.5$  and 2.4 Hz), 7.90 (dd, 1H,  $J = 2.4$  and 8.6 Hz), 7.11-6.94 (m, 4H), 3.37 (q, 2H,  $J = 7.0$  Hz), 2.77 (t, 2H,  $J = 7.2$  Hz), 2.10 (s, 3H), 1.43 (s, 9H).

#### Step 5

{2-[4-(5-Carbamoyl-pyridin-2-yloxy)-3-methyl-phenyl]-ethyl}-carbamic acid *tert*-butyl ester

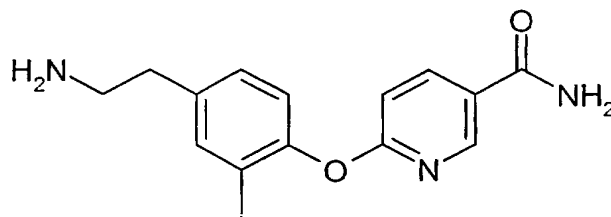


The compound of step 4 is subject to hydrolysis using hydrogen peroxide and potassium carbonate. The details of the hydrolysis procedure to form the amide from nitrile have been described exhaustively somewhere in P-15876.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): 8.58 (d, 1H, J= 2.4 Hz), 8.17 (dd, 1H, J= 2.4 and 8.6 Hz), 7.09-6.90 (m, 4H), 3.38 (q, 2H, J= 6.7 Hz), 2.77 (t, 2H, J= 7.0 Hz), 2.11 (s, 3H), 1.43 (s, 9H).

#### Step 6

6-[4-(2-Amino-ethyl)-2-methyl-phenoxy]-nicotinamide



To a solution of compound of step 5 (376 mg, 1.01 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), trifluoroacetic acid is added (2.03 mL, 26.4 mmol). Stir the reaction mixture at room temperature for 2h. Eliminate the solvent and purify by SCX column to obtain the title compound (264 mg, 96%). Electrospray MS M<sup>+</sup>+1 ion: 272. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.58 (d, 1H, J= 2.4 Hz), 8.24 (dd, 1H, J= 2.7 and 8.9 Hz), 7.17-6.94 (m, 4H), 2.94-2.86 (m, 2H), 2.78-2.71 (m, 2H), 2.10 (s, 3H).

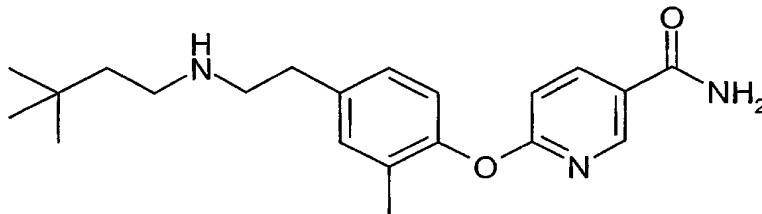
#### Step 7

Combine 3-methyl-butylaldehyde (60μl, 0.22 mmol), amine from step 6 above (60 mg, 0.22 mmol) and 3A molecular sieves (670 mg) in methanol (2 mL), stir the mixture at room temperature overnight. Add NaBH<sub>4</sub> (41 mg, 1.10 mmol) and stir at room temperature for 3 hours. Filtrate the mixture over celite and eliminate the solvent. Purify the crude mixture by flash chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 80/20) to obtain the title compound (45 mg, 60%). Electrospray MS M+1 ion = 342. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.59 (dd, 1H, J= 0.8 and 2.7 Hz), 8.24 (dd, 1H, J= 2.4 and 8.6 Hz), 7.19-7.10 (m, 2H), 7.00-6.93 (m, 2H), 2.93-2.76 (m, 4H), 2.70-2.62 (m, 2H), 2.10 (s, 3H), 1.71-1.36 (m, 3H), 0.91 (d, 6H, J= 6.4 Hz).

By the method of example 1 the following examples (examples 2-8) were prepared. The purification process is described in each case

**Example 652**

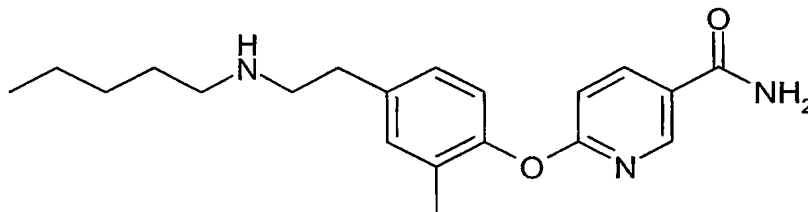
6-{2-Methyl-4-[2-(3,3-dimethyl-butylamino)-ethyl]-phenoxy}-nicotinamide



Purification: SCX column. Electrospray MS M+1 ion = 356. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.59 (d, 1H, J= 2.4 Hz), 8.24 (dd, 1H, J= 2.4 and 8.6 Hz), 7.18-7.10 (m, 2H), 7.00-6.94 (m, 2H), 2.92-2.78 (m, 4H), 2.69-2.60 (m, 2H), 2.10 (s, 3H), 1.48-1.39 (m, 2H), 0.93 (s, 9H).

**Example 653**

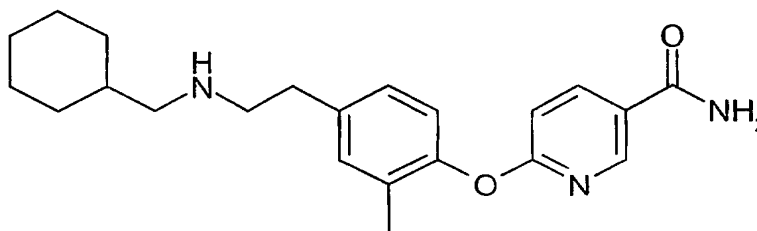
6-[2-Methyl-4-(2-pentylamino-ethyl)-phenoxy]-nicotinamide



Purification: Flash chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>/EtOAc/MeOH:NH<sub>3</sub> 2M 35/60/5). Electrospray MS M+1 ion = 342. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.59 (dd, 1H, J= 0.5 and 2.3 Hz), 8.24 (dd, 1H, J= 2.6 and 8.8 Hz), 7.17-7.08 (m, 2H), 6.98-6.92 (m, 2H), 2.88-2.75 (m, 4H), 2.65-2.57 (m, 2H), 2.09 (s, 3H), 1.59-1.25 (m, 6H), 0.91 (t, 3H, J= 6.4 Hz).

**Example 654**

6-{4-[2-(Cyclohexylmethyl-amino)-ethyl]-2-methyl-phenoxy}-nicotinamide

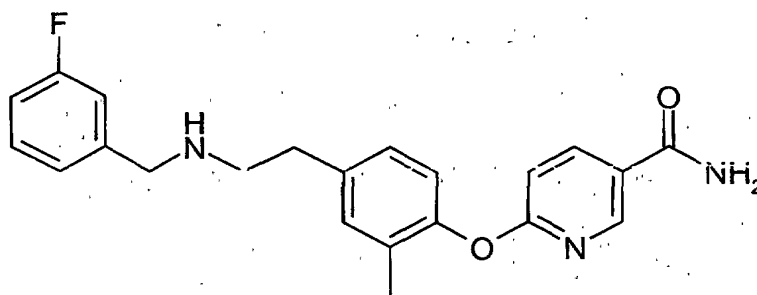




Purification: Flash chromatography (eluent:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90/10). Electrospray MS  $M+1$  ion = 368.  $^1\text{H-NMR}$  (metanol- $d_4$ , 200 MHz): 8.59 (d, 1H,  $J=2.4$  Hz), 8.24 (dd, 1H,  $J=2.7$  and 8.6 Hz), 7.18-7.10 (m, 2H), 7.00-6.93 (m, 2H), 2.85 (bs, 4H), 2.50 (d, 2H,  $J=6.4$  Hz), 2.10 (s, 3H), 1.77-0.84 (m, 11H).

### Example 655

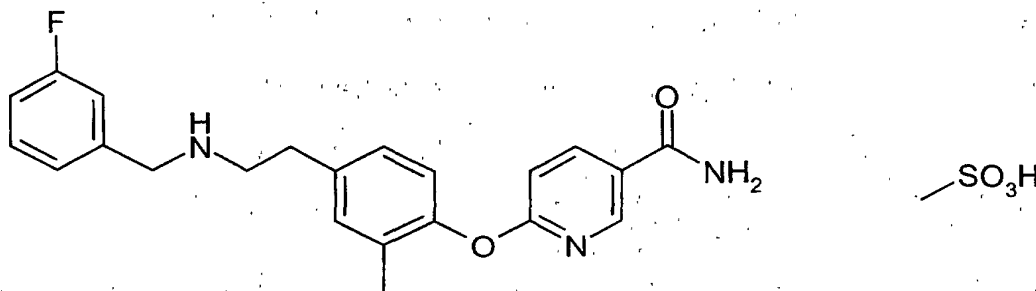
6-{4-[2-(3-Fluoro-benzylamino)-ethyl]-2-methyl-phenoxy}-nicotinamide



Purification: SCX column. Electrospray MS  $M+1$  ion = 380.  $^1\text{H-NMR}$  (metanol- $d_4$ , 200 MHz): 8.59 (dd, 1H,  $J=0.5$  and 2.4 Hz), 8.24 (dd, 1H,  $J=2.4$  and 8.6 Hz), 7.38-6.92 (m, 8H), 3.79 (s, 2H), 2.82 (s, 4H), 2.09 (s, 3H).

### Example 656

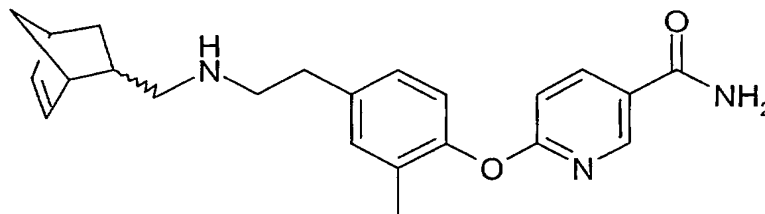
6-{4-[2-(3-Fluoro-benzylamino)-ethyl]-2-methyl-phenoxy}-nicotinamide, mesylate salt



Example 655 (free amine of example 656) was dissolved in THF, then methanesulfonic acid was added (1.0 eq), the mixture was stirred for 1 hour and the solvent eliminated to give the title compound. Electrospray MS  $M+1$  ion = 380.  $^1\text{H-NMR}$  (metanol- $d_4$ , 300 MHz): 8.59 (bs, 1H), 8.28 (dd, 1H,  $J=1.4$  and 8.7 Hz), 7.56-7.02 (m, 8H), 4.30 (s, 2H), 3.36 (t, 2H,  $J=7.3$  Hz), 3.06 (t, 2H,  $J=7.3$  Hz), 2.72 (s, 3H), 2.14 (s, 3H).

**Example 657**

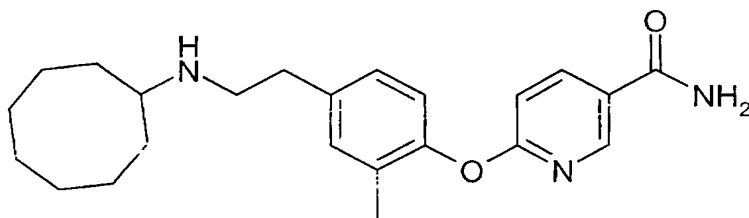
6-(4-{2-[(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-ethyl}-2-methyl-phenoxy)-nicotinamide



Purification: HPLC (Column: X-Terra MS C18. A= 10 mM  $\text{NH}_4\text{HCO}_3$  pH9/B=  $\text{CH}_3\text{CN}$ . Gradient mode: from 30 to 99% B. Flow rate: 1mL/min). Electrospray MS M+1 ion = 378.  $^1\text{H}$ -NMR (methanol- $\text{d}_4$ , 200 MHz): 8.59 (d, 1H, J= 2.6 Hz), 8.24 (dd, 1H, J= 2.4 and 8.6 Hz), 7.16-6.91 (m, 4H), 6.16-5.88 (m, 2H), 2.81-1.81 (m, 9H), 2.09 (s, 3H), 1.65-0.99 (m, 3H), 0.57-0.48 (m, 1H).

**Example 658**

6-[4-(2-Cyclooctylamino-ethyl)-2-methyl-phenoxy]-nicotinamide

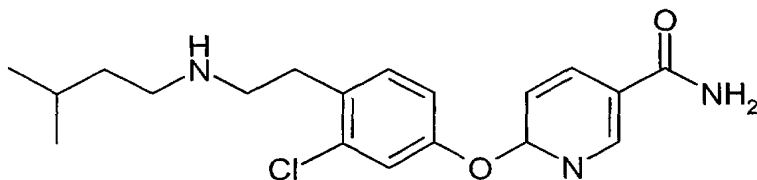


Purification: Flash chromatography (eluent:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  70/30). Electrospray MS M+1 ion = 382.  $^1\text{H}$ -NMR (methanol- $\text{d}_4$ , 200 MHz): 8.59 (d, 1H, J= 2.4 Hz), 8.24 (dd, 1H, J= 2.4 and 8.6 Hz), 7.18-6.92 (m, 4H), 2.95-2.77 (m, 5H), 2.12 (m, 1H), 2.10 (s, 3H), 1.89-1.46 (m, 13H).

**Example 659**

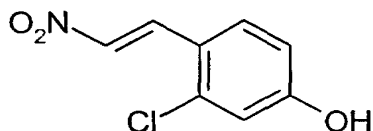
6-{3-Chloro-4-[2-(3-methyl-butylamino)-ethyl]-phenoxy}-nicotinamide

407



Step 1

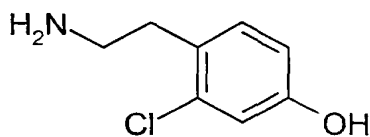
3-Chloro-4-(2-nitro-vinyl)-phenol



The 3-chloro-4-hydroxy-benzaldehyde (980 mg, 6.3 mmol), nitromethane (2.0 mL, 37.7 mmol) and ammonium acetate (1.9 g, 25.1 mmol) were dissolved in acetic acid (9 mL) and the reaction heated at 110°C for 2 h. The reaction is concentrated under reduced pressure and the residue partitioned between ether and water. Separate the layers and dry with Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate under reduced pressure. Purify the crude by flash chromatography (eluent: EtOAc/hexane 20/80 and 30/70) afforded the title compound (1.0 g, 80%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): 8.34 (d, 1H, J= 13.4 Hz), 7.82 (d, 1H, J= 13.4 Hz), 7.71 (d, 1H, J= 8.6 Hz), 6.94 (d, 1H, J= 2.4 Hz), 6.80 (dd, 1H, J= 2.4 and 8.6 Hz).

Step 2

4-(2-Amino-ethyl)-3-choloro-phenol

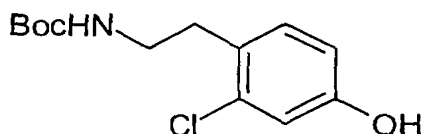


To lithium aluminum hydride 1.0M in ether (1.50 mL, 1.50 mmol) at 0°C a solution of aluminum trichloride (201 mg, 1.51 mmol) in THF (2 mL) is added. After 5 min a solution of compound obtained in step 1 above (100 mg, 0.50 mmol) in THF (2 mL) is added and the reaction is allowed to stir at room temperature overnight. Add water and then 3 N HCl, the aqueous layer is extracted with 3/1 n-butanol/toluene. The combined organic layers are dried over sodium sulfate and concentrated. SCX ion-exchange chromatography afforded 70 mg (81%) of the title compound. Electrospray MS M+1 ion=

172.  $^1\text{H}$ -NMR (methanol- $d_4$ , 200 MHz): 7.06 (d, 1H,  $J$ = 8.3 Hz), 6.79 (d, 1H,  $J$ = 2.4 Hz), 6.65 (dd, 1H,  $J$ = 2.4 and 8.3 Hz), 2.82 (m, 4H).

### Step 3

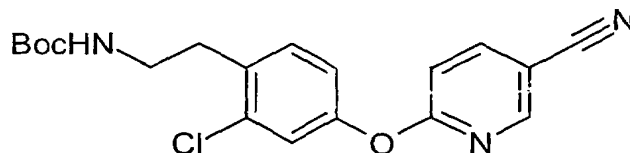
[2-(4-Hydroxy-2-chloro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester



Dissolve amine obtained in step 2 above (620 mg, 3.62 mmol) in dry THF (20 mL) and DMF (1 mL) under  $\text{N}_2$  atmosphere, add a solution of di-*tert*-butyl dicarbonate (791 mg, 3.62 mmol) in THF (10 mL), stir the mixture at room temperature overnight. Eliminate the solvent and purify the crude by flash chromatography (eluent: EtOAc/hexane 30/70) to obtain the title compound (670 mg, 68%). TLC  $R_f$  (EtOAc/hexane 20/80): 0.27.  $^1\text{H}$ -NMR (methanol- $d_4$ , 200 MHz): 7.06 (d, 1H,  $J$ = 8.3 Hz), 6.78 (d, 1H,  $J$ = 2.6 Hz), 6.65 (dd, 1H,  $J$ = 2.4 and 8.3 Hz), 3.21 (t, 2H,  $J$ = 6.7 Hz), 2.78 (t, 2H,  $J$ = 7.5 Hz), 1.41 (s, 9H).

### Step 4

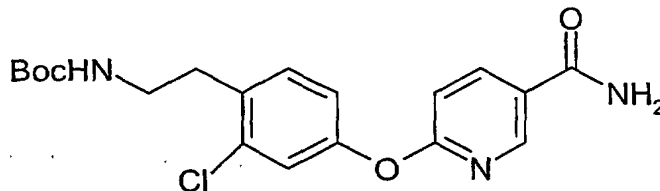
{2-[4-(5-Cyano-pyridin-2-yloxy)-2-chloro-phenyl]-ethyl}-carbamic acid *tert*-butyl ester



A solution of phenol obtained in step 3 above (650 mg, 2.4 mmol), 6-chloronicotinonitrile (333 mg, 2.4 mmol) and sodium hydride (115 mg, 2.9 mmol) in DMSO (12 mL) is stirred at room temperature for 18 h. Pour the mixture into iced water and extract the aqueous layer with EtOAc. Dry the organic layer over  $\text{Na}_2\text{SO}_4$ , filtrate and eliminate the solvent. Purify by flash chromatography (eluent: EtOAc/hexane 20/80 and 30/70) to get the title compound (810 mg, 90%). Electrospray MS  $\text{M}^+ + 1$ -Boc group ion: 318.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 200 MHz): 8.46 (dd, 1H,  $J$ = 0.5 and 2.2 Hz), 7.94 (dd, 1H,  $J$ = 2.4 and 8.6 Hz), 7.31-7.18 (m, 2H), 7.06-6.98 (m, 2H), 3.41 (q, 2H,  $J$ = 6.7 Hz), 2.95 (t, 2H,  $J$ = 7.3 Hz), 1.44 (s, 9H).

### Step 5

{2-[4-(5-Carbamoyl-pyridin-2-yloxy)-2-chloro-phenyl]-ethyl}-carbamic acid *tert*-butyl ester

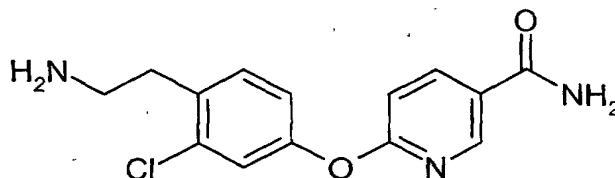


The compound of step 4 is subject to hydrolysis using hydrogen peroxide and potassium carbonate. The details of the hydrolysis procedure to form the amide from nitrile have been described previously.

<sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.62 (dd, 1H, J= 0.8 and 2.7 Hz), 8.27 (dd, 1H, J= 2.4 and 8.6 Hz), 7.34 (d, 1H, J= 8.3 Hz), 7.22 (d, 1H, J= 2.4 Hz), 7.07-7.02 (m, 2H), 3.34 (m, 2H), 2.92 (t, 2H, J= 7.3 Hz), 1.42 (s, 9H).

#### Step 6

6-[4-(2-Amino-ethyl)-2-chloro-phenoxy]-nicotinamide



The compound of step 5 is subject to hydrolysis using trifluoroacetic acid. The details of the hydrolysis procedure to remove the protecting group have been described previously. Electrospray MS M+1 ion= 292. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.60 (dd, 1H, J=0.8 and 2.7 Hz), 8.28 (dd, 1H, J= 2.7 and 8.9 Hz), 7.38 (d, 1H, J= 8.3 Hz), 7.24 (d, 1H, J= 2.4 Hz), 7.09-7.03 (m, 2H), 2.94 (s, 4H).

#### Step 7

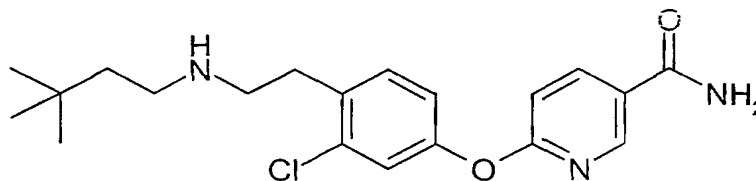
Combine compound from step 6 (60mg, 0.21 mmol), 3-methyl-butyraldehyde (24  $\mu$ L, 0.23 mmol) and 3A molecular sieves (670 mg) in methanol (2 mL), stir the mixture at room temperature overnight. Add NaBH<sub>4</sub> (41 mg, 1.10 mmol) and stir at room temperature for 3 hours. Filtrate the mixture over celite and eliminate the solvent. Purify the crude mixture by SCX to obtain the title compound. Electrospray MS M+1 ion = 362.

<sup>1</sup>H-NMR (metanol-d<sub>4</sub>, 200 MHz): 8.61 (dd, 1H, J= 0.8 and 2.7 Hz), 8.27 (dd, 1H, J= 2.4 and 8.6 Hz), 7.38 (d, 1H, J= 8.6 Hz), 7.22 (d, 1H, J= 2.4 Hz), 7.07-7.03 (m, 2H), 3.03-2.81 (m, 4H), 2.70-2.62 (m, 2H), 1.62 (m, 1H), 1.48-1.37 (m, 2H), 0.92 (d, 6H, J= 6.5 Hz).

By the method of example 9 the following examples (examples 10-14) were prepared. The purification process is described in each case

#### Example 660

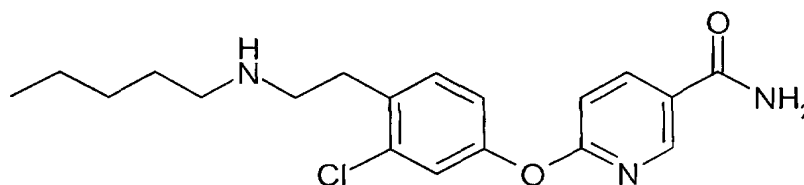
6-{3-Chloro-4-[2-(3,3-dimethyl-butylamino)-ethyl]-phenoxy}-nicotinamide



Purification: SCX column. Electrospray MS M+1 ion = 376. <sup>1</sup>H-NMR (metanol-d<sub>4</sub>, 200 MHz): 8.61 (dd, 1H, J= 0.5 and 2.4 Hz), 8.27 (dd, 1H, J= 2.7 and 8.9 Hz), 7.38 (d, 1H, J= 8.3 Hz), 7.22 (d, 1H, J= 2.4 Hz), 7.09-7.03 (m, 2H), 3.02-2.81 (m, 4H), 2.69-2.61 (m, 2H), 1.49-1.40 (m, 2H), 0.93 (s, 9H).

#### Example 661

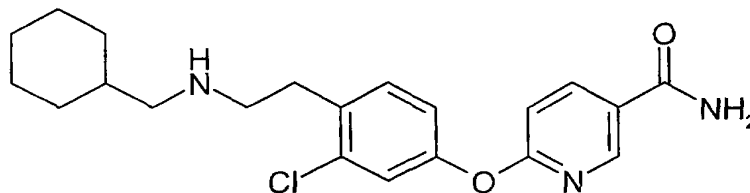
6-[3-Chloro-4-(2-pentylamino-ethyl)-phenoxy]-nicotinamide



Purification: flash chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10). Electrospray MS M+1 ion = 362. <sup>1</sup>H-NMR (metanol-d<sub>4</sub>, 200 MHz): 8.61 (dd, 1H, J= 0.8 and 2.4 Hz), 8.27 (dd, 1H, J= 2.4 and 8.6 Hz), 7.38 (d, 1H, J= 8.3 Hz), 7.23 (d, 1H, J= 2.4 Hz), 7.09-7.03 (m, 2H), 3.03-2.81 (m, 4H), 2.68-2.61 (m, 2H), 1.61-1.47 (m, 2H), 1.37-1.28 (m, 4H), 0.93 (t, 3H, J= 6.7 Hz).

**Example 662**

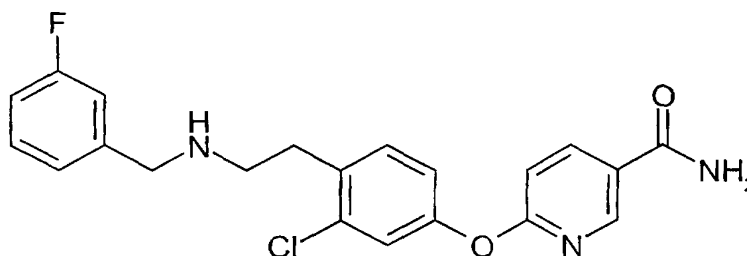
6-{3-Chloro-4-[2-(cyclohexylmethyl-amino)-ethyl]-phenoxy}-nicotinamide



Purification: SCX column. Electrospray MS M+1 ion = 388. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 300 MHz): 8.63 (d, 1H, J= 1.8 Hz), 8.28 (dd, 1H, J= 2.4 and 8.5 Hz), 7.37 (d, 1H, J= 8.2 Hz), 7.22 (d, 1H, J= 2.2 Hz), 7.07-7.03 (m, 2H), 3.01-2.81 (m, 4H), 2.49 (d, 2H, J= 6.7 Hz), 1.79-1.68 (m, 5H), 1.61-1.42 (m, 1H), 1.38-1.17 (m, 3H), 0.99- 0.85 (m, 2H).

**Example 663**

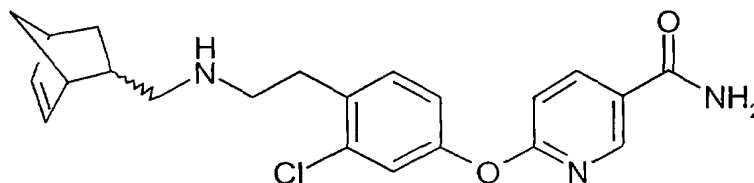
6-{3-Chloro-4-[2-(3-fluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide



Purification: SCX column. Electrospray MS M+1 ion = 400. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 300 MHz): 8.63 (d, 1H, J= 2.2 Hz), 8.27 (dd, 1H, J= 2.4 and 8.7 Hz), 7.36-6.95 (m, 8H), 3.82 (s, 2H), 3.01-2.81 (m, 4H).

**Example 664**

6-(4-{2-[(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-ethyl}-3-chloro-phenoxy)-nicotinamide



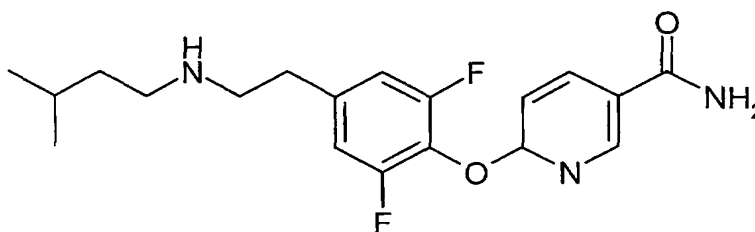
nicotinamide

Purification: SCX column. Electrospray MS M+1 ion = 398. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 8.61 (dd, 1H, J= 0.5 and 2.4 Hz), 8.26 (dd, 1H, J= 2.4 and 8.6 Hz), 7.40-7.03 (m,

4H), 6.18-5.92 (m, 2H), 3.01-2.66 (m, 6H), 2.40-2.18 (m, 2H), 1.95-1.83 (m, 1H), 1.64-1.11 (m, 3H), 0.60-0.50 (m, 1H).

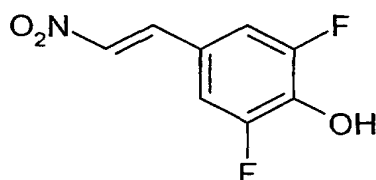
### Example 665

6-{2,6-Difluoro-4-[2-(3-methyl-butylamino)-ethyl]-phenoxy}-nicotinamide



#### Step 1

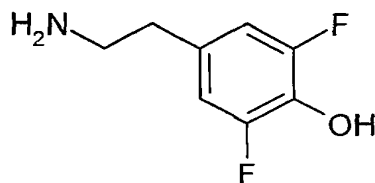
2,6-Difluoro-4-(2-nitro-vinyl)-phenol



Aldehyde (2,6-difluoro-4-hydroxybenzaldehyde) (2.27g, 14.4 mmol), nitromethane (4.7 mL, 86.4 mmol) and ammonium acetate (4.4 g, 57.6 mmol) were dissolved in acetic acid (22 mL) and the reaction heated at 110°C for 1 h 30 min. The reaction is concentrated under reduced pressure and the residue partitioned between ether and water. Separate the layers and dry with Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate under reduced pressure. Purify the crude by flash chromatography (eluent: EtOAc/hexane 22/78) afforded the title compound (2.05 g, yield: 71%). Electrospray MS M-1 ion = 200. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): 7.84 (d, 1H, J= 13.7 Hz), 7.45 (d, 1H, J= 13.7 Hz), 7.19-6.99 (m, 2H).

#### Step 2

4-(2-Amino-ethyl)-2,6-difluoro-phenol



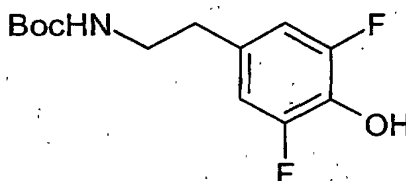
To lithium aluminum hydride 1.0M in ether (30 mL, 29.8 mmol) at 0°C a solution of aluminum trichloride (4.0g, 29.8 mmol) in THF (40 mL) is added. After 5 min a solution



of compound obtained in step 1 above (2.0g, 9.95 mmol) in THF (40 mL) is added and the reaction is allowed to stir at room temperature overnight. Add water and then 3 N HCL, the aqueous layer is extracted with 3/1 n-butanol/toluene. The combined organic layers are dried over sodium sulfate and concentrated. SCX ion-exchange chromatography afforded 1.50 g (87%) of the title compound. Electrospray MS M+1 ion= 174. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 200 MHz): 6.95-6.78 (m, 2H), 3.14 (t, 2H, J= 7.0 Hz), 2.86 (t, 2H, J= 7.3 Hz).

## Step3

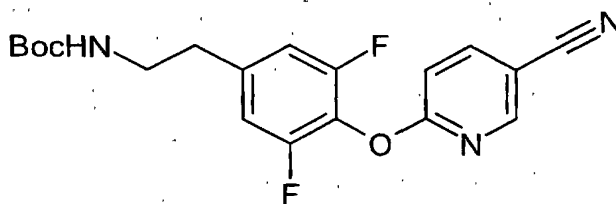
[2-(3,5-Difluoro-4-hydroxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester



Dissolve amine obtained in step 2 above (1.5 g, 8.67 mmol) in dry THF (22 mL) under N<sub>2</sub> atmosphere, add a solution of di-*tert*-butyl dicarbonate (1.89 g, 8.67 mmol) in THF (22 mL), stir the mixture at room temperature overnight. Eliminate the solvent. Purify by flash chromatography (eluent: EtOAc/hexane 1/4 and 1/1) to obtain the desired compound (1.40 g). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): 6.85-6.66 (m, 2H), 3.31 (q, 2H, J= 6.2 Hz), 2.69 (t, 2H, J= 7.0 Hz), 1.44 (s, 9H).

## Step 4

{2-[4-(5-Cyano-pyridin-2-yloxy)-3,5-difluoro-phenyl]-ethyl}-carbamic acid *tert*-butyl ester

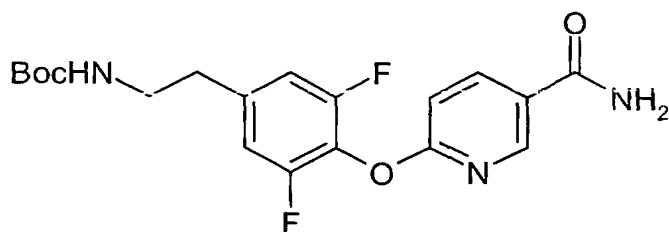


A solution of phenol obtained in step 3 above (1.31 g, 4.8 mmol), 6-chloronicotinonitrile (700 mg, 5.04 mmol) and sodium hydride (290 mg, 7.2 mmol) in DMSO (25 mL) is stirred at room temperature for 18 h. Pour the mixture into iced water and extract the aqueous layer with EtOAc. Dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>, filtrate and eliminate the

solvent. Purify by flash chromatography (EtOAc/hexane 20/80 and 34/66) to get the title compound (950 mg, 51%).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz): 8.41 (dd, 1H,  $J = 0.8$  and 2.1 Hz), 7.97 (dd, 1H,  $J = 2.4$  and 8.6 Hz), 7.18 (dd, 1H,  $J = 0.8$  and 8.6 Hz), 6.92-6.81 (m, 2H), 3.39 (q, 2H,  $J = 6.9$  Hz), 2.81 (t, 2H,  $J = 6.7$  Hz), 1.45 (s, 9H).

## Step 5

{2-[4-(5-Carbamoyl-pyridin-2-yloxy)-3,5-difluoro-phenyl]-ethyl}-carbamic acid *tert*-butyl ester

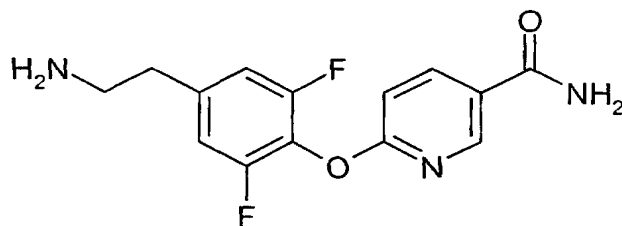


The compound of step 4 is subject to hydrolysis using hydrogen peroxide and potassium carbonate. The details of the hydrolysis procedure to form the amide from nitrile have been described exhaustively somewhere in P-15876.

$^1\text{H-NMR}$  (methanol- $d_4$ , 300 MHz): 8.58 (d, 1H,  $J = 2.4$  Hz), 8.31 (dd, 1H,  $J = 2.4$  and 8.7 Hz), 7.19 (d, 1H,  $J = 8.7$  Hz), 7.02-6.98 (m, 2H), 3.35-3.30 (m, 2H), 2.81 (t, 2H,  $J = 7.1$  Hz), 1.44 (s, 9H).

## Step 6

6-[4-(2-Amino-ethyl)-2,6difluoro-phenoxy]-nicotinamide



To a solution of compound of step 5 (930 mg, 2.37 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL), trifluoroacetic acid is added (4.7 mL, 61.5 mmol). Stir the reaction mixture at room temperature for 2h. Eliminate the solvent and purify by SCX column to obtain the title compound (658 mg, 95%). Electrospray MS  $M^+ + 1$  ion: 294.  $^1\text{H-NMR}$  (methanol- $d_4$ , 200

MHz): 8.56 (d, 1H, J= 2.4 Hz), 8.30 (dd, 1H, J= 2.4 and 8.9 Hz), 7.18 (d, 1H, J= 8.9 Hz), 7.05-6.95 (m, 2H), 2.96-2.74 (m, 4H).

### Step 7

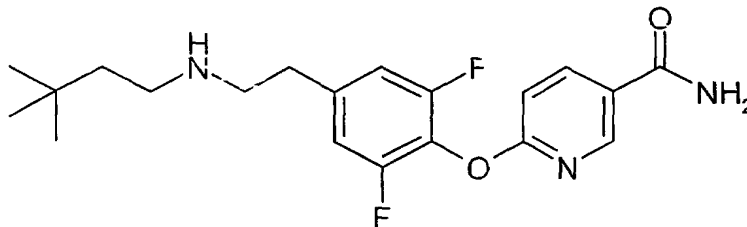
Combine 3-methyl-butylaldehyde (26 $\mu$ l, 0.24 mmol), amine from step 6 above and 3A molecular sieves (900 mg) in methanol (3 mL), stir the mixture at room temperature overnight. Add NaBH<sub>4</sub> (45 mg, 1.20 mmol) and stir at room temperature for 3 hours.

Filtrate the mixture over celite and eliminate the solvent. Submit the crude to a SCX column to obtain a solid which was further purified by HPLC (Column: X-Terra MS C18. A= 10 Mm NH<sub>4</sub>HCO<sub>3</sub> pH8/B= CH<sub>3</sub>CN. Gradient mode: from 30 to 70% B. Flow rate: 1mL/min) to obtain the title compound (42 mg). Electrospray MS M+1 ion = 364. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 300 MHz): 8.60 (d, 1H, J= 2.0 Hz), 8.32 (dd, 1H, J= 2.2 and 8.5 Hz), 7.19 (d, 1H, J= 8.7 Hz), 7.01-6.98 (m, 2H), 2.85 (m, 4H), 2.63 (m, 2H), 1.62 (m, 1H), 1.42 (q, 1H, J= 7.3 Hz), 0.92 (d, 6H, J= 6.5 Hz).

By the method of example 665 the following examples (examples 666-669) were prepared. The purification process is described in each case

### Example 666

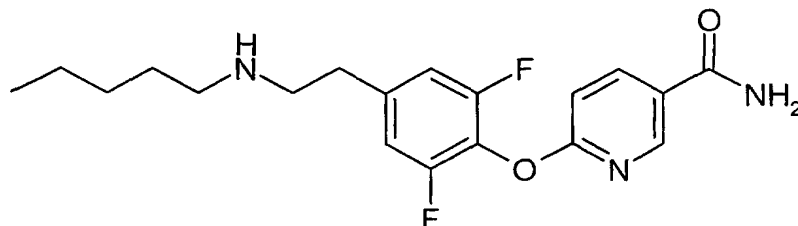
6-{4-[2-(3,3-Dimethyl-butylamino)-ethyl]-2,6-difluoro-phenoxy}-nicotinamide



Purification: HPLC (Column: X-Terra MS C18. A= 10 Mm NH<sub>4</sub>HCO<sub>3</sub> pH8/B= CH<sub>3</sub>CN. Gradient mode: from 30 to 99% B. Flow rate: 1mL/min ). Electrospray MS M+1 ion = 378. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>, 300 MHz): 8.48 (d, 1H, J= 2.4 Hz), 8.23 (dd, 1H, J= 2.4 and 8.5 Hz), 7.12 (d, 1H, J= 8.5 Hz), 7.00-6.93 (m, 2H), 2.91-2.78 (m, 4H), 2.67-2.61 (m, 2H), 1.43-1.38 (m, 2H), 0.87 (s, 9H).

**Example 667**

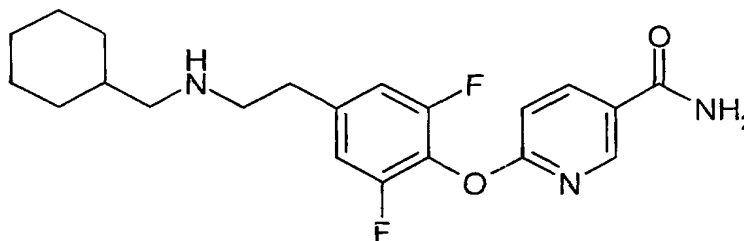
6-[2,6-Difluoro-4-(2-pentylamino-ethyl)-phenoxy]-nicotinamide



Purification: HPLC (Column: X-Terra MS C18. A= 10 Mm NH<sub>4</sub>HCO<sub>3</sub> pH8/B= CH<sub>3</sub>CN. Gradient mode: from 25 to 70% B. Flow rate: 1mL/min). Electrospray MS M+1 ion = 364. <sup>1</sup>H-NMR (metanol-d<sub>4</sub>, 300 MHz): 8.59 (d, 1H, J= 2.4 Hz), 8.32 (dd, 1H, J= 2.4 and 8.7 Hz), 7.19 (d, 1H, J= 8.7 Hz), 7.02-7.00 (m, 2H), 2.88 (m, 4H), 2.65 (t, 2H, J= 7.3 Hz), 1.55 (m, 2H), 1.35 (m, 4H), 0.93 (t, 3H, J= 6.7 Hz).

**Example 668**

6-{4-[2-(Cyclohexylmethyl-amino)-ethyl]-2,6-difluoro-phenoxy}-nicotinamide

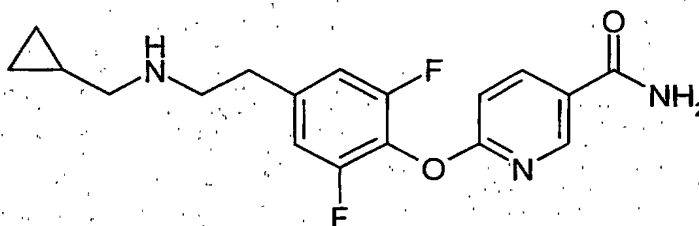


Purification: HPLC (Column: X-Terra MS C18. A= 10 Mm NH<sub>4</sub>HCO<sub>3</sub> pH8/B= CH<sub>3</sub>CN. Gradient mode: from 30 to 99% B. Flow rate: 1mL/min). Electrospray MS M+1 ion = 390. <sup>1</sup>H-NMR (metanol-d<sub>4</sub>, 300 MHz): 8.48 (d, 1H, J= 2.4 Hz), 8.23 (dd, 1H, J= 2.4 and 8.9 Hz), 7.11 (d, 1H, J= 8.8 Hz), 6.99-6.92 (m, 2H), 2.83 (m, 4H), 2.47 (d, 2H, J= 6.9 Hz), 1.72-1.59 (m, 5H), 1.55-1.41 (m, 1H), 1.31-1.05 (m, 3H), 0.94-0.81 (m, 2H).

**Example 669**

6-{4-[2-(Cyclopropylmethyl-amino)-ethyl]-2,6-difluoro-phenoxy}-nicotinamide

417



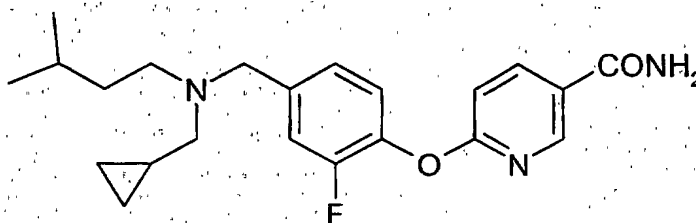
Purification: HPLC (Column: X-Terra MS C18. A= 10 Mm  $\text{NH}_4\text{HCO}_3$  pH8/B= MeOH. Gradient mode: from 35 to 80% B. Flow rate: 1mL/min). Electrospray MS M+1 ion = 348.  $^1\text{H}$ -NMR (methanol- $\text{d}_4$ , 300 MHz): 8.59 (d, 1H, J= 2.4 Hz), 8.32 (dd, 1H, J= 2.4 and 8.7 Hz), 7.19 (d, 1H, J= 8.7 Hz), 7.02-7.00 (m, 2H), 2.93-2.83 (m, 4H), 2.50 (d, 2H, J= 6.9 Hz), 1.10-0.90 (m, 1H), 0.55-0.49 (m, 2H), 0.20-0.15 (m, 2H).

#### **General Procedure: Reductive Amination (Examples 670-693)**

To a mixture of amine (1 equiv), aldehyde (1.5 equiv) in 5% AcOH/methanol (0.2 M) was added  $\text{NaCNBH}_4$  (5 equiv) and the resulting reaction mixture was stirred for 2 hours under nitrogen atmosphere at room temperature. The reaction can be monitored by electrospray MS or TLC. Ethyl acetate was added to the reaction mixture and washed twice with saturated aqueous solution of  $\text{NaHCO}_3$ . The organic layer was separated, dried over anhydrous  $\text{NaSO}_4$  and the solvent evaporated to yield a residue which was purified by flash chromatography using chloroform/ethanol/ $\text{NH}_4\text{OH}$ , 94.5/5/0.5) to afford the title compound as a white solid.

#### **Example 670**

6-[4-((3-Methyl-butyl), cyclopropylmethyl amino methyl)-2-fluoro phenoxy] nicotinamide



The title compound was prepared by reductive amination of 6-[2-fluoro-4-((3-methyl-butyl) aminomethyl)phenoxy]nicotinamide with cyclopropylcarboxaldehyde.

83% Yield. Mp 94-5°C.

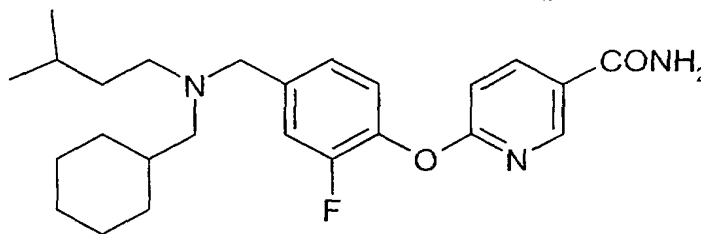
$^1\text{H}$  NMR ( $\text{CHCl}_3-d_3$ )  $\delta$ : 8.55 (d, 1H,  $J = 2.4$  Hz), 8.15 (dd, 1H,  $J = 8.5, 2.4$  Hz), 7.28-7.10 (m, 3H), 6.98 (d, 1H,  $J = 8.5$  Hz), 6.53 (bs, 2H), 3.62 (s, 2H), 2.56 (t, 2H,  $J = 7.4$  Hz), 2.33 (d, 2H,  $J = 7.4$  Hz), 1.65-1.55 (m, 1H), 1.55-1.40 (m, 2H), 0.85 (d, 6H+1H,  $J = 6.5$  Hz), 0.47 (m, 2H), 0.53 (m, 2H).

$^{13}\text{C}$  NMR ( $\text{CHCl}_3-d_3$ )  $\delta$ : 167.9, 165.4, 156.4, 153.1, 147.6, 139.7, 139.3, 125.0, 123.5, 117.3, 110.9, 59.0, 58.0, 52.3, 36.2, 26.6, 23.1, 8.9, 4.3.

MS (Electrospray): 386.2 ( $\text{M}^+ + 1$ ).

### Example 671

6-[4-((3-Methyl-butyl), cyclohexylmethyl amino methyl)-2-fluoro phenoxy] nicotinonamide



The title compound was prepared by reductive amination of 6-[2-fluoro-4-((3-methyl-butyl) aminomethyl)phenoxy]nicotinamide with cyclohexylcarboxaldehyde.

71% Yield. Mp 110-1°C

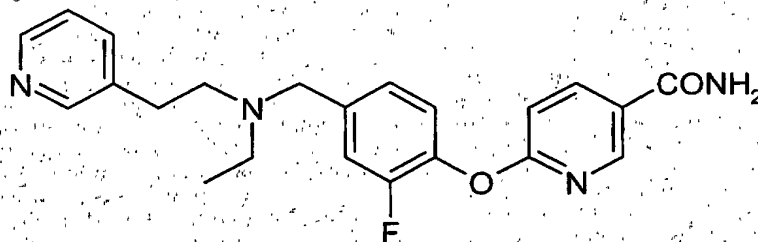
$^1\text{H}$  NMR ( $\text{CHCl}_3-d_3$ )  $\delta$ : 8.55 (d, 1H,  $J = 2.3$  Hz), 8.15 (dd, 1H,  $J = 8.6, 2.3$  Hz), 7.28-7.10 (m, 3H), 6.98 (d, 1H,  $J = 8.6$  Hz), 6.37 (bs, 2H), 3.49 (s, 2H), 2.49 (t, 2H,  $J = 7.2$  Hz), 2.15 (d, 2H,  $J = 7.2$  Hz), 1.75-1.10 (m, 13H), 1.55-1.40 (m, 2H), 0.83 (d, 6H+1H,  $J = 6.6$  Hz).

$^{13}\text{C}$  NMR ( $\text{CHCl}_3-d_3$ )  $\delta$ : 167.8, 165.5, 156.4, 153.1, 147.5, 139.7, 139.1, 124.9, 123.5, 117.2, 110.9, 69.0, 61.8, 58.9, 52.9, 43.0, 36.5, 32.2, 29.9, 26.5, 23.0.

MS (Electrospray): 428.4 ( $\text{M}^+ + 1$ ).

**Example 672**

6-[4-(((3-Pyridylethyl), ethyl amino methyl)-2-fluoro phenoxy] nicotinonamide



The title compound was prepared by reductive amination of 6-[2-fluoro-4-((3-methyl-butyl) aminomethyl)phenoxy]nicotinamide with acetaldehyde.

51% Yield.

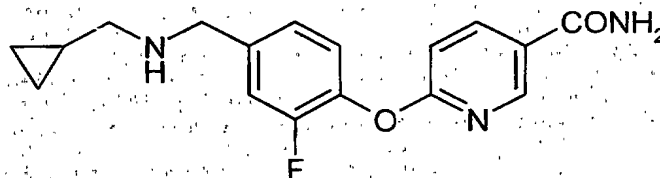
$^1\text{H}$  NMR ( $\text{CHCl}_3\text{-}d_3$ )  $\delta$ : 8.58 (bs, 1H), 8.40 (bs, 2H), 8.20 (dd, 1H,  $J = 8.9, 2.4$  Hz), 7.45 (d, 1H,  $J = 7.7$  Hz), 7.25 (dd, 1H,  $J = 7.9, 3.8$  Hz), 7.15-7.00 (m, 4H), 6.80 (bs, 1H), 6.20 (bs, 1H), 3.59 (s, 2H), 2.70 (m, 4H), 2.55 (c, 2H,  $J = 7.0$  Hz), 1.04 (t, 3H,  $J = 7.0$  Hz).

$^{13}\text{C}$  NMR ( $\text{CHCl}_3\text{-}d_3$ )  $\delta$ : 167.7, 165.3, 156.4, 153.1, 150.3, 147.6, 139.8, 139.5, 139.4, 139.3, 136.8, 136.4, 125.0, 124.7, 123.6, 116.9, 110.9, 57.6, 57.7, 47.7, 31.3, 12.2.

MS (Electrospray): 395.4 ( $\text{M}^+ + 1$ ).

**Example 673**

6-[4-(Cyclopropyl methyl amino methyl)-2-fluoro phenoxy] nicotinonamide



The title product was prepared following standard reductive amination techniques with cyclopropylmethyl amine and 6-(4-formyl-2-fluorophenoxy)nicotinamide.

58% Yield. MP 128-9°C

$^1\text{H}$  NMR ( $\text{MeOH-}d_4$ )  $\delta$ : 8.60 (d, 1H,  $J = 2.4$  Hz), 8.27 (dd, 1H,  $J = 8.7, 2.4$  Hz), 7.33-7.18 (m, 3H), 6.98 (d, 1H,  $J = 8.7$  Hz), 3.81 (s, 2H), 2.44 (d, 1H,  $J = 6.7$  Hz), 1.00 (m, 1H), 0.51 (m, 2H), 0.16 (m, 2H).

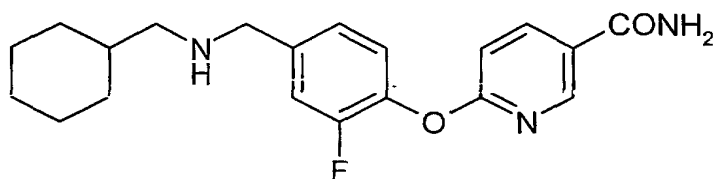
$^{13}\text{C}$  NMR (MeOH- $d_4$ )  $\delta$ : 170.0, 166.6, 157.9, 154.6, 149.1, 141.0, 140.7, 126.8, 126.3, 125.3, 118.2, 111.8, 55.2, 53.7, 11.8, 4.5.

MS (Electrospray): 316.1 ( $\text{M}^+ + 1$ ).

#### Example 674

6-[4-(Cyclohexyl methyl amino methyl)-2-fluoro phenoxy] nicotinamide

The title product was prepared following standard reductive amination techniques with cyclohexylmethyl amine and 6-(4-formyl-2-fluorophenoxy)nicotinamide.



58% Yield. MP 152-3°C.

$^1\text{H}$  NMR (MeOH- $d_4$ )  $\delta$ : 8.60 (d, 1H,  $J = 2.2$  Hz), 8.26 (dd, 1H,  $J = 8.5, 2.2$  Hz), 7.35-7.15 (m, 3H), 7.01 (d, 1H,  $J = 8.7$  Hz), 3.78 (s, 2H), 2.45 (d, 1H,  $J = 6.7$  Hz), 1.90-1.65 (m, 5H), 1.55 (m, 1H), 1.45-1.15 (m, 3H), 1.00-0.80 (m, 2H).

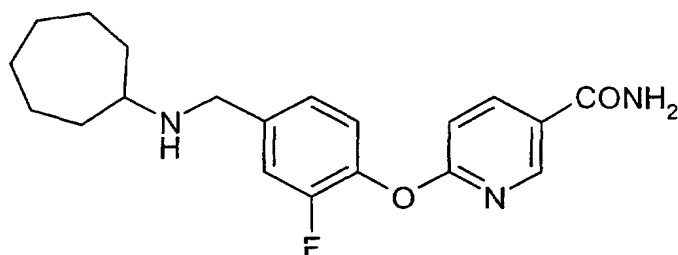
$^{13}\text{C}$  NMR (MeOH- $d_4$ )  $\delta$ : 170.0, 166.7, 157.9, 154.6, 149.1, 141.2, 140.8, 126.8, 126.3, 125.3, 118.2, 111.7, 57.0, 54.1, 39.2, 32.9, 28.1, 27.5.

MS (Electrospray): 358.1 ( $\text{M}^+ + 1$ ).



**Example 675****6-[4-(Cycloheptylamino methyl)-2-fluoro phenoxy] nicotinonamide**

The title product was prepared following standard reductive amination techniques with cycloheptylamine and 6-(4-formyl-2-fluorophenoxy)nicotinamide.

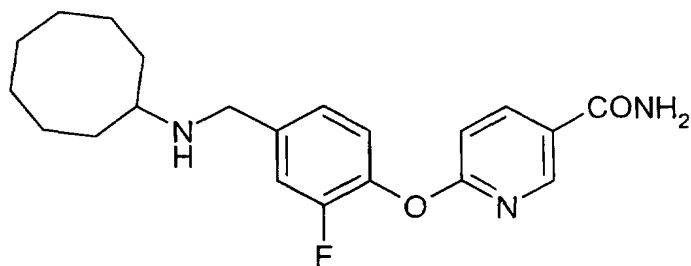


69% Yield.

$^1\text{H}$  NMR (MeOH- $d_4$ )  $\delta$ : 8.59 (d, 1H,  $J = 2.2$  Hz), 8.26 (dd, 1H,  $J = 8.5, 2.2$  Hz), 7.34-7.18 (m, 3H), 7.10 (d, 1H,  $J = 8.7$  Hz), 3.80 (s, 2H), 2.75 (bs, 1H), 1.85-1.70 (m, 5H), 1.70-1.35 (m, 7H).

$^{13}\text{C}$  NMR (MeOH- $d_4$ )  $\delta$ : 170.0, 166.7, 157.9, 154.6, 149.1, 141.2, 126.8, 126.4, 126.3, 125.3, 118.3, 111.7, 58.3, 34.9, 28.6, 27.4, 25.8.

MS (Electrospray): 358.1 ( $\text{M}^+ + 1$ ).

**Example 676****6-[4-(Cyclooctylamino methyl)-2-fluoro phenoxy] nicotinonamide**

The title product was prepared following standard reductive amination techniques with cyclooctylamine and 6-(4-formyl-2-fluorophenoxy)nicotinamide in 49% Yield.

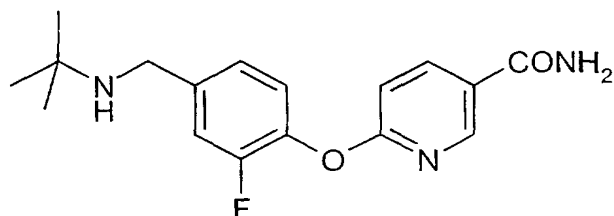
$^1\text{H}$  NMR ( $\text{MeOH-}d_4$ )  $\delta$ : 8.59 (d, 1H,  $J = 2.4$  Hz), 8.26 (dd, 1H,  $J = 8.7, 2.4$  Hz), 7.40-7.20 (m, 3H), 7.08 (d, 1H,  $J = 8.7$  Hz), 3.78 (s, 2H), 2.68 (bs, 1H), 2.00-1.85 (m, 2H), 1.80-1.40 (m, 14H).

$^{13}\text{C}$  NMR ( $\text{MeOH-}d_4$ )  $\delta$ : 170.0, 166.7, 157.9, 154.6, 149.1, 141.1, 140.9, 126.8, 126.3, 125.3, 118.2, 111.7, 59.6, 51.4, 38.8, 35.6, 29.7, 26.0.

MS (Electrospray): 372.3 ( $\text{M}^+ + 1$ ).

### Example 677

6-[4-(*tert*-butylamino methyl)-2-fluoro phenoxy] nicotinonamide



The title product was prepared following standard reductive amination techniques with *tert*-butylamine and 6-(4-formyl-2-fluorophenoxy)nicotinamide in 12 % yield.

$^1\text{H}$  NMR ( $\text{MeOH-}d_4$ )  $\delta$ : 8.58 (d, 1H,  $J = 2.4$  Hz), 8.27 (dd, 1H,  $J = 8.7, 2.4$  Hz), 7.35-7.20 (m, 3H), 7.10 (d, 1H,  $J = 8.7$  Hz), 3.75 (s, 2H), 1.22 (s, 9H).

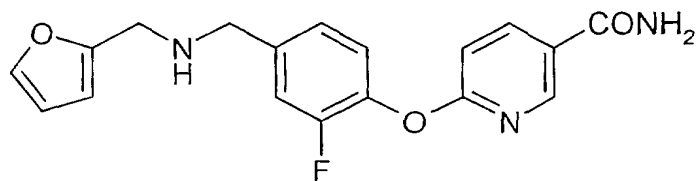
$^{13}\text{C}$  NMR ( $\text{MeOH-}d_4$ )  $\delta$ : 170.1, 166.7, 157.6, 154.6, 149.0, 141.6, 141.5, 126.8, 126.4, 125.3, 118.4, 111.6, 52.4, 47.5, 29.1.

MS (Electrospray): 318.1 ( $\text{M}^+ + 1$ ).

### Example 678

6-[4-(2-furylmethyl amino methyl)-2-fluoro phenoxy] nicotinonamide

The title product was prepared following standard reductive amination techniques with 2-furylmethylamine and 6-(4-formyl-2-fluorophenoxy)nicotinamide.



27% Yield.

$^1\text{H}$  NMR (MeOH- $d_4$ )  $\delta$ : 8.60 (d, 1H,  $J = 2.0$  Hz), 8.26 (dd, 1H,  $J = 8.7, 2.0$  Hz), 7.46 (bs, 1H), 7.30-7.15 (m, 3H), 7.08 (d, 1H,  $J = 8.5$  Hz), 6.37 (bs, 1H), 6.29 (bs, 1H), 3.77 (s, 4H).

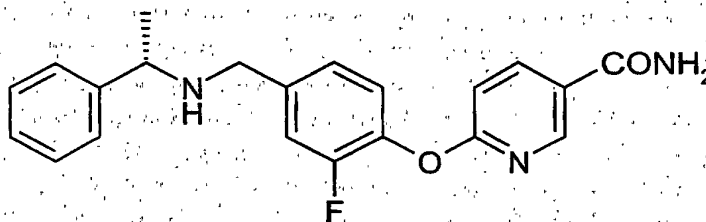
$^{13}\text{C}$  NMR (MeOH- $d_4$ )  $\delta$ : 170.0, 166.7, 158.0, 154.8, 149.1, 143.7, 141.2, 140.5, 140.4, 126.8, 126.4, 126.3, 125.3, 118.3, 111.7, 109.1, 52.9, 46.0.

MS (Electrospray): 342.1 ( $\text{M}^+ + 1$ ).

### Example 679

(S)-6-[4-(Methylbenzyl amino methyl)-2-fluorophenoxy] nicotinonamide

The title compound prepared following standard reductive amination with (S)-methylbenzylamine and 6-(4-formyl-2-fluorophenoxy)nicotinamide.



50% Yield.

$^1\text{H}$  NMR (MeOH- $d_4$ )  $\delta$ : 8.59 (d, 1H,  $J = 2.0$  Hz), 8.30 (dd, 1H,  $J = 8.5, 2.0$  Hz), 7.40-7.30 (m, 4H), 7.28 (m, 1H), 7.18 (m, 2H), 7.09 (m, 2H), 3.81 (c, 1H,  $J = 6.7$  Hz), 3.60 (AB system, 2H), 1.39 (d, 3H,  $J = 6.7$  Hz).

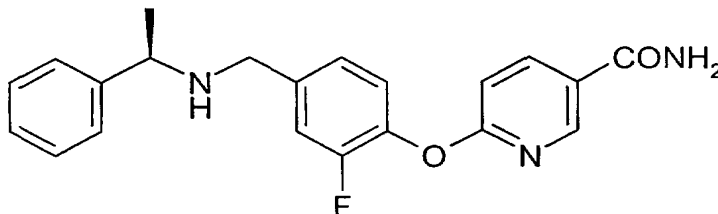
$^{13}\text{C}$  NMR (MeOH- $d_4$ )  $\delta$ : 170.1, 166.7, 157.9, 154.6, 149.0, 146.4, 141.2, 130.0, 128.4, 127.2, 126.8, 126.3, 126.2, 125.2, 118.1, 111.7, 58.9, 51.7, 24.5.

MS (Electrospray): 366.1 ( $\text{M}^+ + 1$ ).

**Example 680**

(R)-6-[4-(Methylbenzyl amino methyl)-2-fluoro phenoxy] nicotinamide

The title compound was prepared following standard reductive amination with (R)-methylbenzylamine and 6-(4-formyl-2-fluorophenoxy)nicotinamide.



39% Yield.

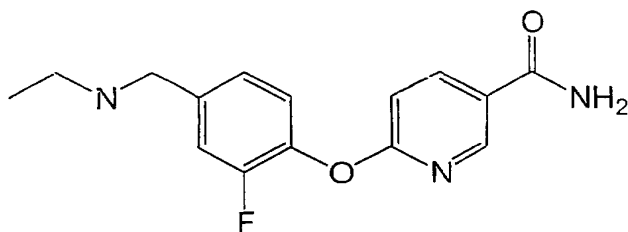
$^1\text{H}$  NMR (MeOH- $d_4$ )  $\delta$ : 8.59 (d, 1H,  $J = 2.0$  Hz), 8.30 (dd, 1H,  $J = 8.5, 2.0$  Hz), 7.40-7.30 (m, 4H), 7.28 (m, 1H), 7.18 (m, 2H), 7.09 (m, 2H), 3.81 (c, 1H,  $J = 6.7$  Hz), 3.60 (AB system, 2H), 1.39 (d, 3H,  $J = 6.7$  Hz).

$^{13}\text{C}$  NMR (MeOH- $d_4$ )  $\delta$ : 170.1, 166.7, 157.9, 154.6, 149.0, 146.4, 141.2, 130.0, 128.4, 127.2, 126.8, 126.3, 126.2, 125.2, 118.1, 111.7, 58.9, 51.7, 24.5.

MS (Electrospray): 366.1 ( $\text{M}^+ + 1$ ).

**Example 681**

Synthesis of 6-(4-Ethylaminomethyl-2-fluoro-phenoxy)-nicotinamide



Using ethylamine and 2-fluoro-4-

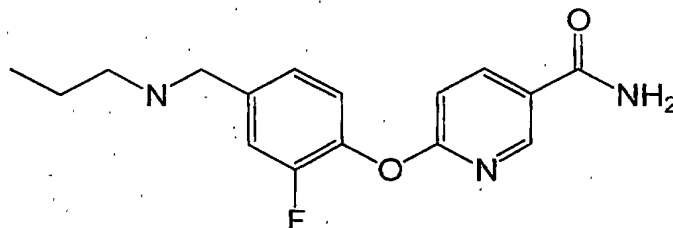
formylphenoxy nicotinamide, the title product was obtained in 72% Yield

$^1\text{H}$  NMR (DMSO, 300 MHz)  $\delta$ : 8.54 (dd,  $J = 1.8$ , 1H), 8.27 (dd,  $J = 7.4, 1.6$  Hz, 1H), 8.00 (br s, 1H), 7.46 (br s, 1H), 7.3-7.1 (m, 4H), 3.68 (s, 2H), 2.49 (q, 2H), 1.02 (t,  $J = 4.6$  Hz, 3H).

MS (Electrospray): ( $\text{M}^+ + 1$ ) 290.2

**Example 682**

Synthesis of 6-(2-Fluoro-4-propylaminomethyl-phenoxy)-nicotinamide



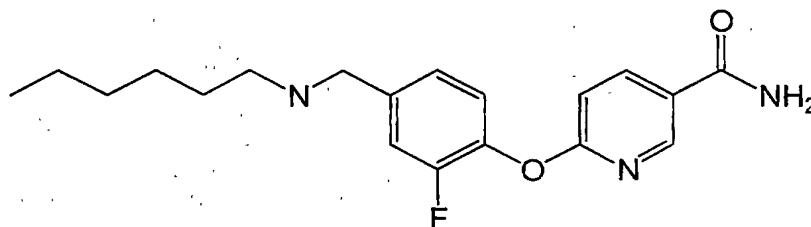
Using n-propylamine and 2-fluoro-4-formylphenoxy nicotinamide, the title product was obtained.

MS (Electrospray): ( $M^+ + 1$ ) 304.2 ( $M^+ - 1$ ) 302.3

HPLC = 90% @ 5.66m (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6mmx15cmx5micron,  $\lambda$ =254nm.de

**Example 683**

Synthesis of 6-(2-Fluoro-4-hexylaminomethyl-phenoxy)-nicotinamide



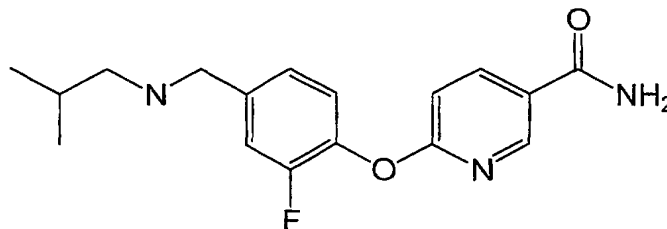
Using hexylamine and 2-fluoro-4-formylphenoxy nicotinamide, the title product was obtained.

MS (Electrospray): ( $M^+ + 1$ ) 346.2 ( $M^+ - 1$ ) 344.4

HPLC = 98% @ 5.98m (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6mmx15cmx5micron,  $\lambda$ =254nm.de

**Example 684**

Synthesis of 6-[2-Fluoro-4-(isobutylamino-methyl)-phenoxy]-nicotinamide



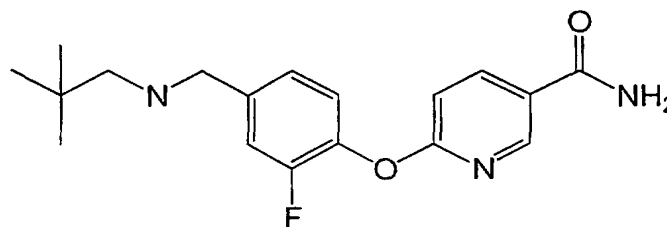
Using isopropylamine and 2-fluoro-4-formylphenoxy nicotinamide, the title product was obtained.

MS (Electrospray): ( $M^+ + 1$ ) 318.2

HPLC = 94% @ 5.72m (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6mmx15cmx5micron,  $\lambda$ =254nm.de

**Example 685**

Synthesis of 6-[2-Fluoro-4-(isobutylamino-methyl)-phenoxy]-nicotinamide



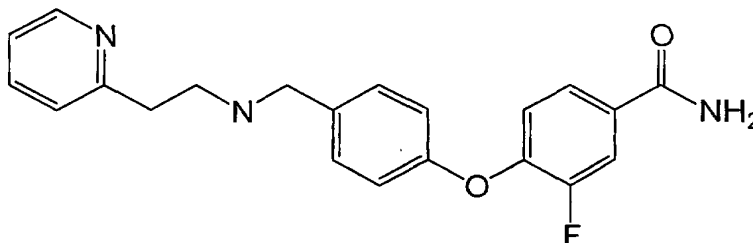
Using 2,2-dimethylpropyl amine and 2-fluoro-4-formylphenoxy nicotinamide, the title product was obtained.

MS (Electrospray): ( $M^+ + 1$ ) 332.2 ( $M^+ - 1$ ) 330.4

HPLC = 99% @ 5.79m (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6mmx15cmx5micron,  $\lambda$ =254nm.de

**Example 686**

Synthesis of 3-Fluoro-4-{4-[(2-pyridin-2-yl-ethylamino)-methyl]-phenoxy}-benzamide



Using 2-pyridino-2-ethylamine and 4-formylphenoxy-3-fluorobenzamide (Example 243, step3), the title product was obtained in 52% Yield.

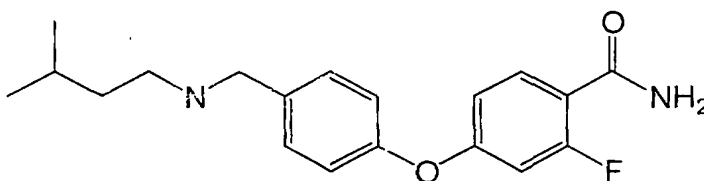
$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 300 MHz)  $\delta$ : 8.41 (d,  $J = 1.8$ , 1H), 8.37 (dd,  $J = 4.8, 1.5$  Hz, 1H), 7.78 (d,  $J = 1.8$ , 1H), 7.74-7.64 (m, 2H), 7.38-7.33 (m, 3H), 7.07-6.97 (m, 3H), 3.77 (s, 2H), 2.85 (s, 4H).

HPLC = 94% @ 5.56m (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6mmx15cmx5micron,  $\lambda=254\text{nm}$ .de

MS (Electrospray): ( $\text{M}^++1$ ) 366.1 ( $\text{M}^+-1$ ) 364.3

**Example 687**

Synthesis of 2-Fluoro-4-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide



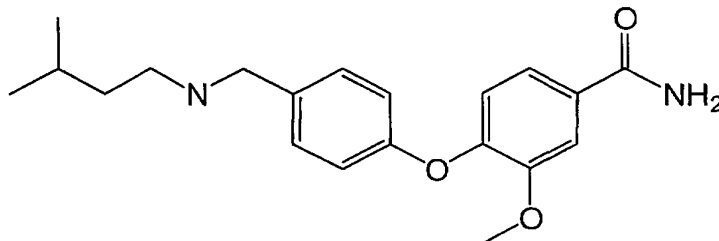
Using 3-methylbutylamine and 4-formylphenoxy-2-fluorobenzamide, the title product was obtained in 10% Yield.

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 300 MHz)  $\delta$ : 7.82 (m, 1H), 7.42 (d,  $J = 8.7\text{Hz}$ , 2H), 7.07 (d,  $J = 8.7\text{Hz}$ , 2H), 6.83 (dd,  $J = 6.9, 2.1\text{Hz}$ , 1H), 6.72 (dd,  $J = 12.6, 2.1\text{Hz}$ , 1H), 3.77 (s, 2H), 2.65-2.59 (m, 2H), 1.66-1.57 (m, 1H), 1.47-1.40 (m, 2H), 0.91 (d,  $J = 6.6\text{Hz}$ , 6H).

MS (Electrospray): ( $\text{M}^++1$ ) 331.2

**Example 688**

Synthesis of 3-Methoxy-4-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide



Using 3-methylbutylamine and 4-formylphenoxy-3-methoxybenzamide, the title product was obtained in 15% Yield.

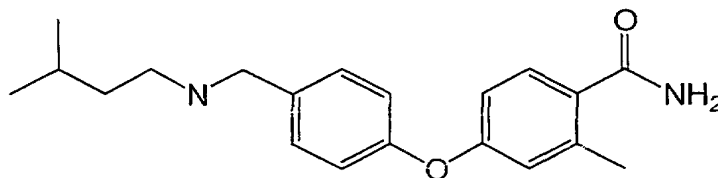
$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 300 MHz)  $\delta$ : 7.62 (d,  $J = 2.4$  Hz, 1H), 7.46 (dd,  $J = 8.1, 1.8$  Hz, 1H), 7.30 (d,  $J = 8.7$ , 2H), 6.96 (d,  $J = 8.1$ , 1H), 6.88 (d,  $J = 8.4$ , 2H), 3.77 (s, 2H), 2.62-2.57 (m, 2H), 1.65-1.56 (m, 1H), 1.46-1.38 (m, 2H), 0.90 (d,  $J = 6.6$  Hz, 6H).

MS (Electrospray): ( $\text{M}^+ + 1$ ) 343.25

HPLC = 98% @ 5.95m (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6mmx15cmx5micron,  $\lambda = 254\text{nm}$ .de

**Example 689**

Synthesis of 2-Methyl-4-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide



Using 3-methylbutylamine and 4-formylphenoxy-2-methylbenzamide, the title product was obtained in 71% Yield.

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 300 MHz)  $\delta$ : 7.42 (d,  $J = 8.4$  Hz, 1H), 7.36 (d,  $J = 6.6$  Hz, 2H), 6.97 (d,  $J = 8.4$ , 2H), 6.67-6.83 (m, 2H), 3.74 (s, 2H), 2.65-2.58 (m, 2H), 2.40 (s, 3H), 1.63-1.59 (m, 1H), 1.47-1.39 (m, 2H), 0.91 (d,  $J = 6.6$  Hz, 6H).

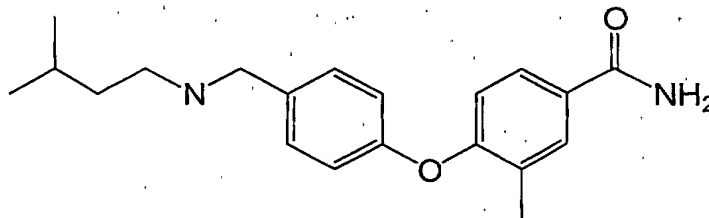
MS (Electrospray): ( $\text{M}^+ + 1$ ) 341.3 ( $\text{M}^+ - 1$ ) 239.4

HPLC = 91% @ 6.07m (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6mmx15cmx5micron,  $\lambda = 254\text{nm}$ .de



**Example 690**

Synthesis of 3-Methyl-4-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide



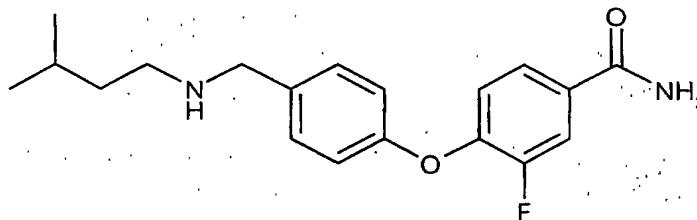
Using 3-methylbutylamine and 4-formylphenoxy-3-methylbenzamide, the title product was obtained in 60% Yield.

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 300 MHz)  $\delta$ : 7.81 (d,  $J$  = 0.9 Hz, 1H), 7.68-7.64 (m 1H), 7.35 (d,  $J$  = 6.6, 2H), 6.92 (d,  $J$  = 6.6, 2H), 6.81 (d,  $J$  = 6.6, 1H), 3.75 (s, 2H), 2.64-2.60 (m, 2H), 2.31 (s, 3H), 1.64-1.60 (m, 1H), 1.47-1.41 (m, 2H), 0.92 (d,  $J$  = 6.6 Hz, 6H).

MS (Electrospray): ( $\text{M}^+$ +1) 327.2

**Example 691**

3-Fluoro-4-{4-[3-methylbutylamino)-methyl]phenoxy}-benzamide



Reductive amination using the intermediate of Example 243 step 3, and 3-methylbutylamine, afforded the title compound in 96% Yield

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 200 MHz)  $\delta$ : 7.76 (dd,  $J$  = 11.6, 2.2 Hz, 1H), 7.69-7.63 (m, 1H), 7.36 (d,  $J$  = 6.7 Hz, 2H), 7.08-6.97 (m, 3H), 3.73 (s, 2H), 2.65-2.55 (m, 2H), 1.67-1.53 (m, 1H), 1.47-1.36 (m, 2H), 0.90 (d,  $J$  = 6.4 Hz, 6H).

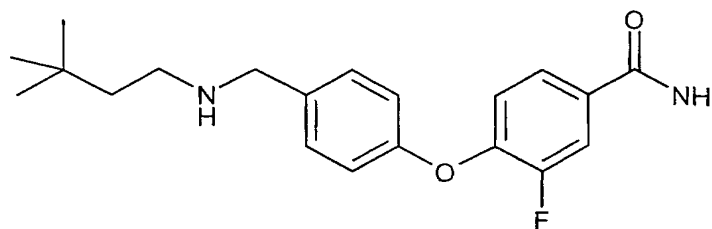
HPLC = 98% @ 6.00m (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6mmx15cmx5micron,  $\lambda$ =254nm.de

MS (APCI): ( $\text{M}^+$ +1) 331.1

**Example 692**

3-Fluoro-4-{4-[(3,3-Dimethyl-butylamino)-methy]-phenoxy}-3-fluoro-benzamide

430



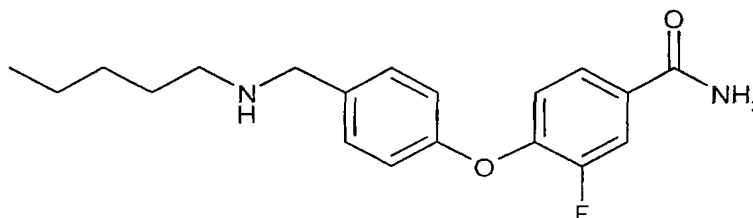
Reductive amination using the intermediate of Example 243 step 3, and 3,3-dimethylbutylamine, afforded the title compound in 62% Yield

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 200 MHz)  $\delta$ : 7.76 (dd,  $J = 11.6, 2.2$  Hz, 1H), 7.74-7.64 (m, 1H), 7.36 (d,  $J = 6.7$  Hz, 2H), 7.08-6.97 (m, 3H), 3.73 (s, 2H), 2.64-2.56 (m, 2H), 1.49-1.41 (m, 2H), 2.1(s, 9H).

MS (APCI): ( $\text{M}^+ + 1$ ) 345.2

### Example 693

3-Fluoro-4-(4-pentylaminomethyl-phenoxy)-benzamide



Reductive amination using the intermediate of Example 243 step 3, and pentylamine, afforded the title compound in 94% Yield.

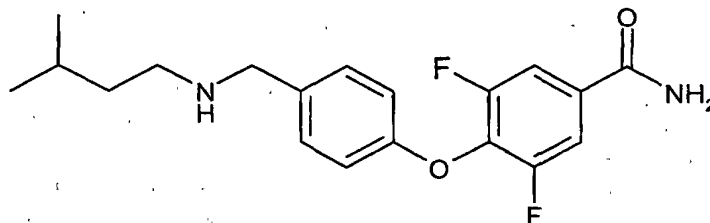
$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 200 MHz)  $\delta$ : 7.77 (dd,  $J = 11.6, 2.2$  Hz, 1H), 7.74-7.69 (m, 1H), 7.36 (d,  $J = 6.7$  Hz, 2H), 7.08-6.97 (m, 3H), 3.73 (s, 2H), 2.60-2.53 (m, 2H), 1.57-1.50 (m, 2H), 1.39-1.29 (m, 4H), 0.91(t,  $J = 6.7$  Hz, 3H).

MS (APCI): ( $\text{M}^+ + 1$ ) 331.1

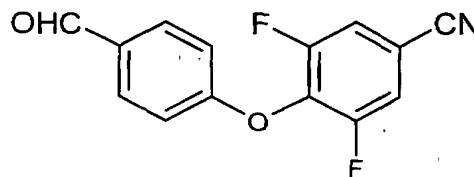
### Example 694

3,5-Difluoro-4-{4-[3-methyl-butylamino)-methyl]-phenoxy}-benzamide

431



## Step 1



## 3,5-Difluoro-4-(4-formyl-phenoxy)benzonitrile

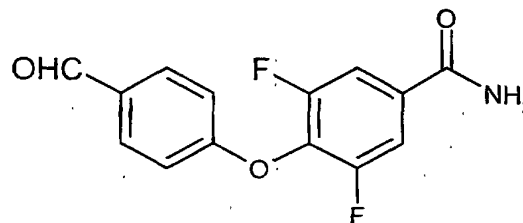
Basic displacement reaction of 4-hydroxy benzaldehyde and 3,5-difluorobenzonitrile using potassium carbonate in anhydrous DMF at reflux temperatures affords the above compound.

76% Yield

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ : 9.93 (s, 1H), 7.87 (d,  $J = 8.8$  Hz, 2H), 7.38 (d,  $J = 6.6$  Hz, 2H), 7.04 (d,  $J = 8.4$  Hz, 2H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 189.9, 157.4, 152.0 (d,  $^1J_{\text{CF}} = 252.1$ ), 146.9 (d,  $^2J_{\text{CF}} = 11.0$ ), 132.2, 132.0, 129.0, 128.7, 128.6, 120.3, 120.0, 119.9 (d,  $^3J_{\text{CF}} = 1.4$ ), 116.7, 116.3 (d,  $^3J_{\text{CF}} = 2.3$ ), 107.1 (d,  $^2J_{\text{CF}} = 8.1$ ), 15.0.

## Step 2



## 3,5-Difluoro-4-(4-formyl-phenoxy)benzamide

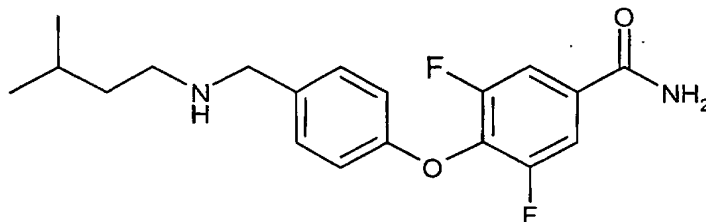
Hydrolysis of the compound of step 1 using hydrogen peroxide and potassium carbonate in DMSO as described previously afford the above compound in 99% yield.

$^1\text{H}$  NMR (DMSO, 200 MHz)  $\delta$ : 9.89 (s, 1H), 8.15 (brs, 1H), 7.90 (d,  $J = 8.8$  Hz, 2H), 7.80 (d,  $J = 8.8$  Hz, 2H), 7.71 (brs, 1H), 7.18 (d,  $J = 8.8$  Hz, 2H).

MS (APCI): ( $\text{M}^+ + 1$ ) 278.0 ( $\text{M}^+ - 1$ ) 276.0

## Step 3

3,5-Difluoro-4-{4-[3-methyl-butylamino]-methyl]-phenoxy}-benzamide



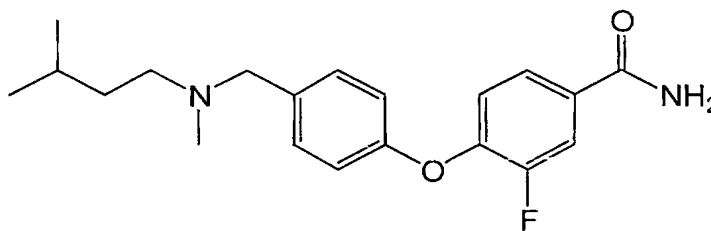
Reductive amination of the compound of step2 with 3-methylbutylamine affords the tittel compound in 61% Yield

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 200 MHz)  $\delta$ : 7.66 (d,  $J = 8.9$  Hz, 2H), 7.31 (d,  $J = 8.6$  Hz, 2H), 6.91 (d,  $J = 8.6$  Hz, 2H), 3.70 (s, 2H), 2.60-2.53 (m, 2H), 1.66-1.49 (m, 1H), 1.46-1.35 (m, 2H), 0.89(d,  $J = 6.4$  Hz, 6H).

MS (APCI): ( $\text{M}^+ + 1$ ) 349.1

## Example 695

Synthesis of 3-Fluoro-4-(4-{[methyl-(3-methyl-butyl)-amino]-methyl}-phenoxy)-benzamide



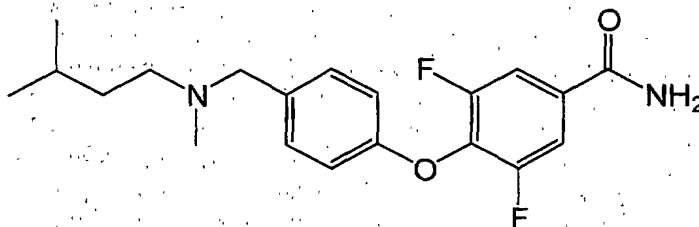
Reductive amination using formaldehyde and the compound of Example 691 affords the title product.

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 300 MHz)  $\delta$ : 7.76 (dd,  $J = 11.4, 1.8$  Hz, 1H), 7.68-7.65 (m, 1H), 7.34 (d,  $J = 6.6$ , 2H), 7.08 (m, 1H), 7.00 (d,  $J = 6.6$ , 2H), 3.51 (s, 2H), 2.44-2.39 (m, 2H), 2.20 (s, 3H), 1.60-1.55 (m, 1H), 1.47-1.39 (m, 2H), 0.90 (d,  $J = 6.6$  Hz, 6H).

MS (Electrospray): ( $\text{M}^+ + 1$ ) 345.2 ( $\text{M}^+ - 1$ ) 343.3

**Example 696**

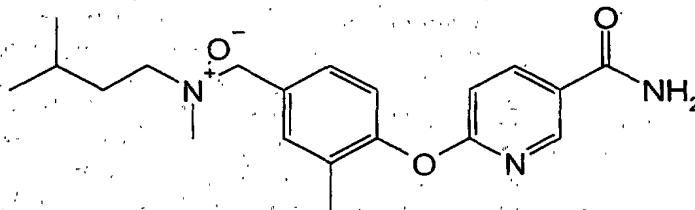
Synthesis of 3,5-Difluoro-4-(4-[[methyl-(3-methyl-butyl)-amino]-methyl]-phenoxy)-benzamide



Reductive amination using formaldehyde and the compound of Example 694, step3 affords title product in 66% Yield.

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 300 MHz)  $\delta$ : 7.66 (d,  $J$  = 9.0 Hz, 2H), 7.28 (d,  $J$  = 8.4 Hz, 2H), 6.90 (d,  $J$  = 8.4 Hz, 2H), 3.47 (s, 2H), 2.41-2.36 (m, 2H), 2.17 (s, 3H), 1.60-1.50 (m, 1H), 1.45-1.39 (m, 2H), 0.88 (d,  $J$  = 6.6 Hz, 6H).

MS (Electrospray): ( $M^+$ +1) 363.2 ( $M^+$ -1) 361.3

**Example 697**

Synthesis of

To a solution of Example 227 in chloroform was added m-CPBA (1.01 equiv) and the reaction mixture stirred for 6 hours at room temperature. It was quenched with few drops of sodium bicarbonate. The organic phase was separated and dried over magnesium sulphate, filtered and concentrated to yield a white solid. Purify by eluting through a 5 g ISCO® column CHCl<sub>3</sub>: 30 % (EtOH : NH<sub>4</sub>OH 10 %) to afford the title compound as a solid.

20% Yield

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 300 MHz)  $\delta$ : 8.59 (dd,  $J$  = 1.8, 0.9 Hz, 1H), 8.28-8.25 (m, 1H), 7.55 (s, 1H), 7.46 (d,  $J$  = 8.4 Hz, 1H), 7.11 (d,  $J$  = 8.1 Hz, 1H), 7.03 (d,  $J$  = 8.7 Hz, 1H), 4.37

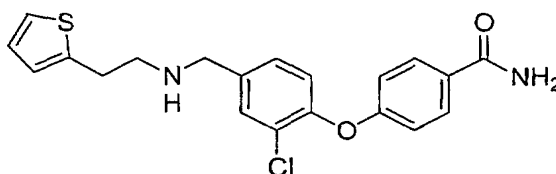
(q, 2H), 3.12-3.07 (m, 2H), 2.99 (s, 3H), 2.17 (s, 3H), 2.00-1.80 (m, 1H), 1.81-1.70 (m, 1H), 1.69-1.60 (m, 1H), 0.98 (dd,  $J = 6.6, 1.2$  Hz, 6H).

MS (Electrospray): ( $M^+ + 1$ ) 358.1 ( $M^+ - 1$ ) 356.3

HPLC = 90% @ 5.94m (5/95 to 95/5 ACN/(0.1%TFA in water) over 10 minutes, Zorbax SB-Phenyl 4.6mmx15cmx5micron,  $\lambda = 254$ nm.de

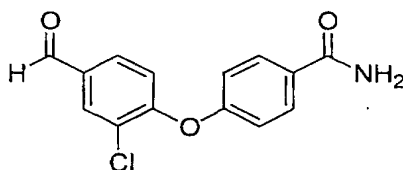
### Example 698

4-{2-Chloro-4-[(2-thiophen-2-yl-ethylamino)-methyl]-phenoxy}-benzamide



#### Step 1: Preparation of Intermediate 1

4-(2-Chloro-4-formyl-phenoxy)-benzamide



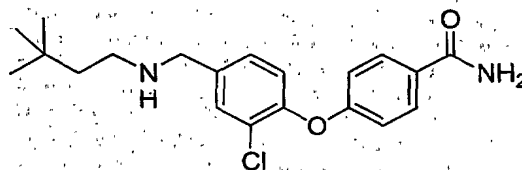
Mix 3-chloro-4-fluorobenzaldehyde (3.28 g, 20.7 mmol), 4-hydroxybenzamide (3.12 g, 22.7 mmol), potassium carbonate (4.29 g, 31.0 mmol) and dimethylacetamide (80 mL) in a flask. Heat the reaction to 100 °C for 3 hours. Let cool to ambient (room) temperature and pour into water (200 mL). After trituration, filter the solid formed and dry on a vacuum pump to obtain the product (5.35 g, 94%).  $^1\text{H}$  NMR (DMSO- $d_6$ ) 9.94 (s, 1H), 8.13 (d,  $J = 1.7$  Hz, 1H), 7.98 (bs, 1H), 7.94 (d,  $J = 8.5$  Hz, 2H), 7.88 (dd,  $J = 1.7$  Hz, 8.5 Hz, 1H), 7.36 (bs, 1H), 7.21 (d,  $J = 8.5$  Hz, 1H), 7.14 (d,  $J = 8.5$  Hz, 2H).

Step 2:

Mix 4-(2-chloro-4-formyl-phenoxy)-benzamide (0.19 g, 0.70 mmol), 2-thiophen-2-yl-ethylamine (0.074 mL, 0.63 mmol), and methanol (8 mL) in a 20 mL vial. After the reaction mixture solubilizes, add 3Å molecular sieves (0.50 g) and stir for 8 hrs. Cool in an ice bath for 10 min and add sodium borohydride (0.048 g, 1.27 mmol). Remove ice bath and stir for 2 hrs. Purify by placing directly onto an SCX column (5 g) using methanol to load and wash and 2M NH<sub>3</sub> in CH<sub>3</sub>OH as eluant to obtain the product (0.23 g, 94%), serial number 2136018. Mass spectrum (ion spray):  $m/z$  = 387.2 (M+1); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 7.89 (bs, 1H), 7.86 (d, J = 8.5 Hz, 2H), 7.57 (s, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.30-7.26 (m, 2H), 7.16 (d, J = 8.8 Hz, 1H), 6.95-6.84 (m, 4H), 3.74 (s, 2H), 2.94 (t, J = 7.1 Hz, 2H), 2.75 (t, J = 7.1 Hz, 2H).

### Example 699

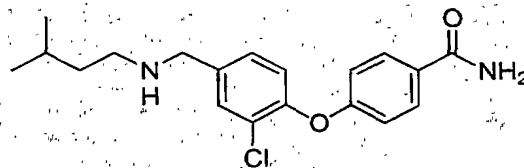
4-{2-Chloro-4-[(3,3-dimethyl-butylamino)-methyl]-phenoxy}-benzamide



Reductive amination of the compound of Example 698, Step1 and 3,3,dimethylbutylamine affords the title product (0.21 g, 99%). Mass spectrum (ion spray):  $m/z$  = 361.3 (M+1); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 7.89 (bs, 1H), 7.86 (d, J = 7.7 Hz, 2H), 7.56 (s, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.28 (bs, 1H), 7.16 (d, J = 7.7 Hz, 1H), 6.89 (d, J = 7.7 Hz, 2H), 3.69 (s, 2H), 2.49 (t, J = 7.7 Hz, 2H), 1.35 (t, J = 7.7 Hz, 2H), 0.85 (s, 9H).

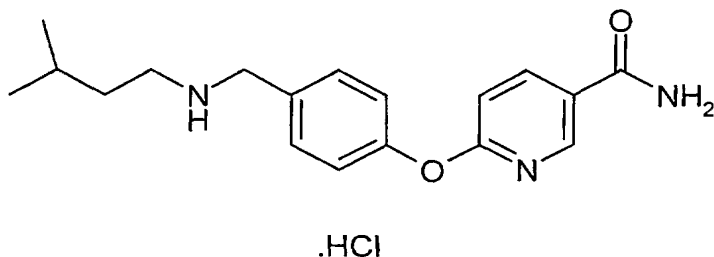
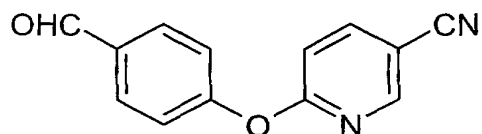
### Example 700

4-{2-Chloro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide

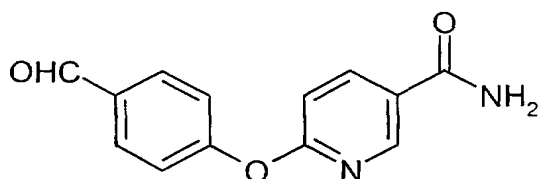


Reductive amination of the compound of Example 698, Step1 and 3-methylbutylamine affords the title product (0.20 g, 92%). Mass spectrum (ion spray):  $m/z$  = 347.3 (M+1); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 7.90 (bs, 1H), 7.86 (d, J = 8.3 Hz, 2H), 7.55 (s, 1H), 7.33 (d, J = 8.3

Hz, 1H), 7.28 (bs, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.89 (d, J = 8.3 Hz, 2H), 3.67 (d, J = 6.7 Hz, 2H), 2.46 (t, J = 7.8 Hz, 2H), 1.61 (septet, J = 6.7 Hz, 1H), 1.30 (q, J = 6.7 Hz, 2H), 0.83 (d, J = 6.7 Hz, 6H).

**Example 701****Step 1**

4-Hydroxybenzaldehyde (2.94 mol), 2-chloro-5-cyanopyridine (2.94mol) and approximately 5.7L of dimethylacetamide were stirred under nitrogen atmosphere. Potassium carbonate ( 6.17mol) was added and the mixture was heated, the at about 100 °C for about 4 hours or until complete as determined by HPLC analysis. The mixture was stirred overnight at room temperature. The product was precipitated by adding ice water and allowing to cool with stirring. The product was filtered and the wetcake was rinsed with water. After air drying, the product was further dried under vacuum at 50 °C.

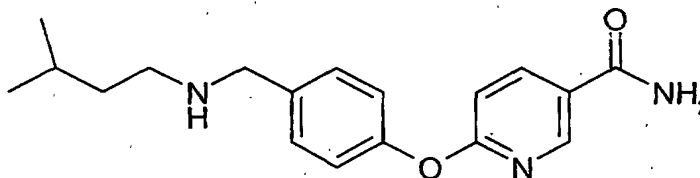
**Step 2**

The product of step1 (2.86mol), potassium carbonate (1.42mol), and DMSO (2.6L) were stirred at room temperature. The mixture was then cooled to 18 °C in an ice-bath,



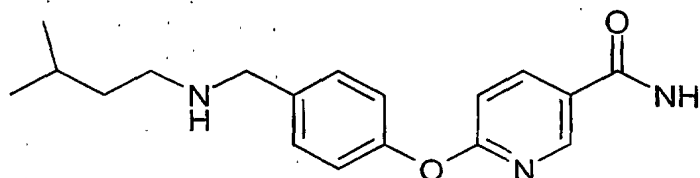
followed by the dropwise addition of 30% hydrogen peroxide (321mL, 3.14mol). The observed exotherm was controlled to 52 °C by a slow peroxide addition rate and adding more ice to the ice-bath. The progress of the reaction was monitored by HPLC which showed consumption of the nitrile. The mixture was allowed to warm to room temperature, poured into ice water (about 13L) and stirred for 45 minutes. The mixture was vacuum filtered and rinsed with water (2 x 3L). The solid was further dried in a vacuum oven at 50°C for 3 days to afford approximately 80% yield.

Step 3:



The product of step 2 (2.28mol), 672 grams of activated molecular sieves, and isopentylamine (3.42mol) were stirred in methanol (12.5L) at room temperature. The mixture was stirred overnight (approximately 16 hours) at room temperature. Upon consumption of the aldehyde as determined by HPLC analysis, sodium borohydride ((34.50g) was added as a solid in 25 gram portions until used up. The reaction mixture was stirred overnight at room temperature and worked as described previously (adjusting for larger amounts of compound) following procedures described previously. To afford about a 93% step 3 yield.

Step 4



.HCl

The product of step 3 (1.66mol) was dissolved in 95:5 EtOH/H<sub>2</sub>O solvents. The solution was heated to 60 °C followed by addition 1N HCl solution (1.66L) over 15 minutes at 60 °C. An additional 500 mL of 95:5 ethanol/water was added to rinse in all of the HCl

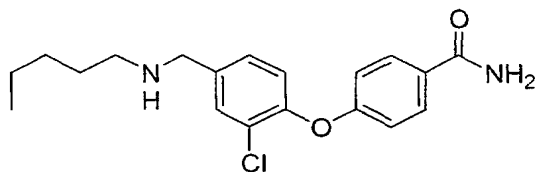
solution. The resulting mixture was stirred at 60 °C for 2 hours. The mixture was allowed to cool to room temperature. The mixture was filtered and the solid was rinsed with 4 x 500mL 95:5 ethanol/water. The solid was dried in a vacuum overnight at 45 °C until drying loss was negligible. Step 4 yield was about 93%.

Mass spectrum (ion spray):  $m/z = 314.7$  ( $M+1$ ),  $^1\text{H}$  NMR  $\delta$  (ppm) 1.03 (d, 6H), 1.78 (s, 3H), 3.40 (s, 2H), 4.54 (s, 2H), 7.41-7.50 (m, 5H), 7.82-7.85 (m, 2H), 9.06-9.08 (m, 1H), 9.23-9.25 (m, 1H).

$^{13}\text{C}$  NMR:  $\delta$  (ppm) 20.56, 25.78, 34.71, 48.06, 51.67, 112.88, 121.58, 125.66, 130.98, 133.30, 140.45, 148.98, 152.17, 161.58, 166.30.

### Example 702

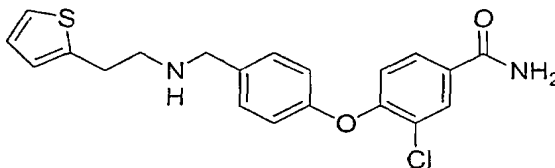
4-(2-Chloro-4-pentylaminomethyl-phenoxy)-benzamide



Reductive amination of the compound of Example 698, Step 1 and pentylamine affords the title product (0.22 g, 98%). Mass spectrum (ion spray):  $m/z = 347.3$  ( $M+1$ );  $^1\text{H}$  NMR (DMSO- $d_6$ ) 7.89 (bs, 1H), 7.86 (d,  $J = 8.9$  Hz, 2H), 7.55 (s, 1H), 7.33 (d,  $J = 8.4$  Hz, 1H), 7.27 (bs, 1H), 7.15 (d,  $J = 8.4$  Hz, 1H), 6.89 (d,  $J = 8.9$  Hz, 2H), 3.67 (s, 2H), 2.45 (t,  $J = 6.7$  Hz, 2H), 1.45-1.37 (m, 2H), 1.28-1.23 (m, 4H), 0.87-0.82 (m, 3H).

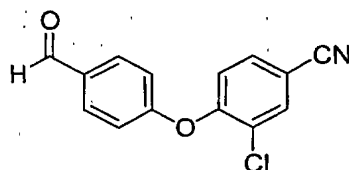
### Example 703

3-Chloro-4-{4-[(2-thiophen-2-yl-ethylamino)-methyl]-phenoxy}-benzamide



Step 1: 3-Chloro-4-(4-formyl-phenoxy)-benzonitrile

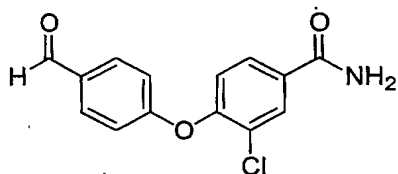
439



Mix 4-hydroxy-benzaldehyde (0.86 g, 7.07 mmol), 3-chloro-4-fluorobenzonitrile (1.00 g, 6.43 mmol), cesium carbonate (3.14 g, 9.64 mmol) and dimethylacetamide (30 mL) in a flask. Heat to 100 °C for 4 hrs. Let cool to room temperature (rt) and pour into water (200 mL). After trituration, filter the solid formed and dry on a vacuum pump to obtain the product (1.57 g, 95%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 9.96 (s, 1H), 8.29 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.6 Hz, 2H), 7.89 (dd, J = 1.8 Hz, 8.6 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H).

Step 2:

3-Chloro-4-(4-formylphenoxy)-benzamide



Cool a solution of 3-chloro-4-(4-formylphenoxy)-benzonitrile (1.57 g, 6.10 mmol) in dimethylsulfoxide (50 mL) to 0 °C. Add potassium carbonate (0.42 g, 3.05 mmol) followed by 30% aqueous hydrogen peroxide (1.83 mL, 6.10 mmol). Remove the cooling bath and let stir at rt for 3 hrs. Pour into water (100 mL) and after trituration, filter the solid formed to obtain the product (1.40 g, 84%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 9.93 (s, 1H), 8.12 (d, J = 1.2 Hz, 1H), 8.10 (bs, 1H), 7.95-7.90 (m, 3H), 7.53 (bs, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.13 (d, J = 8.6 Hz, 2H).

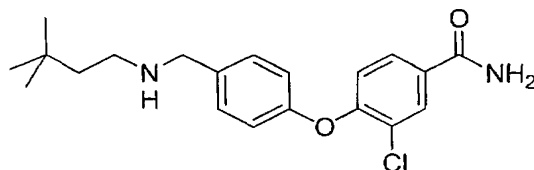
Step 3:

Use 3-chloro-4-(4-formylphenoxy)-benzamide (0.20 g, 0.71 mmol), 2-thiophen-2-ylethylamine (0.075 mL, 0.64 mmol), sodium borohydride (0.049 g, 1.29 mmol) and methanol (8 mL) in a procedure and purification similar to that of Example 1, to obtain the product (0.24 g, 94%), serial number 2137632. Mass spectrum (ion spray): m/z = 387.1 (M+1); <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.93 (d, J = 2.1 Hz, 1H), 7.62 (dd, J = 2.1 Hz, 8.7 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 5.2 Hz, 1H), 6.97 (d, J = 8.3 Hz, 2H), 6.93 (dd,

$J = 3.4$  Hz,  $5.1$  Hz,  $1\text{H}$ ),  $6.88$  (d,  $J = 8.7$  Hz,  $1\text{H}$ ),  $6.84$  (d,  $J = 3.1$  Hz,  $1\text{H}$ ),  $6.11$  (bs,  $2\text{H}$ ),  $3.81$  (s,  $2\text{H}$ ),  $3.05$  (t,  $J = 6.7$  Hz,  $2\text{H}$ ),  $2.95$  (t,  $J = 6.7$  Hz,  $2\text{H}$ ).

#### Example 704

3-Chloro-4-{4-[(3,3-dimethyl-butylamino)-methyl]-phenoxy}-benzamide

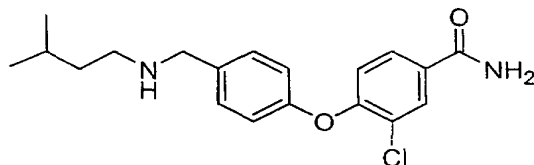


Reductive amination of the compound of Example 703, Step 2 and

3,3-dimethylbutylamine affords the title product (0.21 g, 98%). Mass spectrum (ion spray):  $m/z = 361.2$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $7.93$  (s,  $1\text{H}$ ),  $7.61$  (d,  $J = 7.9$  Hz,  $1\text{H}$ ),  $7.33$  (d,  $J = 7.5$  Hz,  $2\text{H}$ ),  $6.97$  (d,  $J = 7.5$  Hz,  $2\text{H}$ ),  $6.87$  (d,  $J = 8.3$  Hz,  $1\text{H}$ ),  $6.24$  (bs,  $2\text{H}$ ),  $3.78$  (s,  $2\text{H}$ ),  $2.65$  (t,  $J = 6.5$  Hz,  $2\text{H}$ ),  $1.43$  (t,  $J = 6.5$  Hz,  $2\text{H}$ ),  $0.89$  (s,  $9\text{H}$ ).

#### Example 705

3-Chloro-4-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide

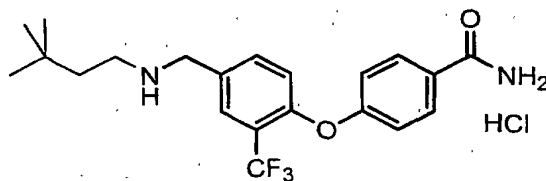


Preparation using a method similar to Example 703 yields the product (0.21 g, 93). Mass spectrum (ion spray):  $m/z = 347.2$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $7.93$  (s,  $1\text{H}$ ),  $7.61$  (d,  $J = 8.4$  Hz,  $1\text{H}$ ),  $7.31$  (d,  $J = 8.4$  Hz,  $2\text{H}$ ),  $6.95$  (d,  $J = 8.4$  Hz,  $2\text{H}$ ),  $6.85$  (d,  $J = 8.6$  Hz,  $1\text{H}$ ),  $6.49$  (bs,  $2\text{H}$ ),  $3.76$  (s,  $2\text{H}$ ),  $2.63$  (t,  $J = 7.3$  Hz,  $2\text{H}$ ),  $1.61$  (septet,  $J = 6.5$  Hz,  $1\text{H}$ ),  $1.39$  (q,  $J = 7.3$  Hz,  $2\text{H}$ ),  $0.87$  (d,  $J = 6.8$  Hz,  $6\text{H}$ ).

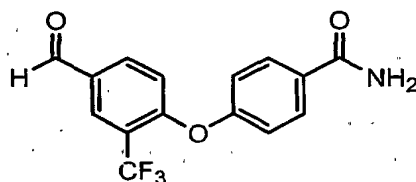
#### Example 706

4-{4-[(3,3-Dimethyl-butylamino)-methyl]-2-trifluoromethyl-phenoxy}-benzamide hydrochloride

441

**Step1**

4-(4-Formyl-2-trifluoromethyl-phenoxy)-benzamide



Preparation using a method similar to Example 703, step 2 yields the product (2.00 g, 88%).  $^1\text{H}$  NMR (DMSO- $d_6$ ) 10.02 (s, 1H), 8.33 (s, 1H), 8.14 (d,  $J = 8.6$  Hz, 1H), 8.00 (bs, 1H), 7.97 (d,  $J = 8.6$  Hz, 2H), 7.39 (bs, 1H), 7.22 (d,  $J = 8.6$  Hz, 2H), 7.19 (d,  $J = 8.6$  Hz, 1H).

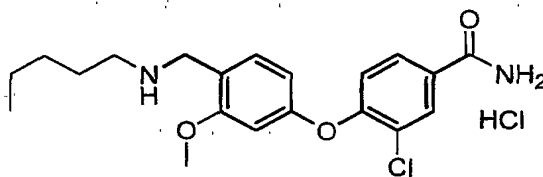
**Step 2**

Preparation using a method similar to Example 697 yields the product (0.17 g, 83%).

Mass spectrum (ion spray):  $m/z = 395.2$  ( $M+1$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.79 (d,  $J = 8.2$  Hz, 2H), 7.66 (s, 1H), 7.48 (d,  $J = 8.4$  Hz, 1H), 7.00–6.94 (m, 3H), 6.33 (bs, 2H), 3.81 (s, 2H), 2.65 (t,  $J = 8.2$  Hz, 2H), 1.43 (t,  $J = 8.2$  Hz, 2H), 0.89 (s, 9H).

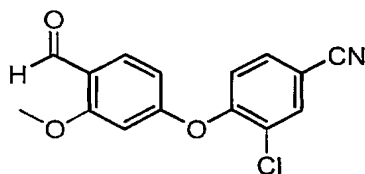
**Example 707**

3-Chloro-4-(3-methoxy-4-pentylaminomethyl-phenoxy)-benzamide hydrochloride

**Step1:**

3-Chloro-4-(4-formyl-3-methoxy-phenoxy)-benzonitrile

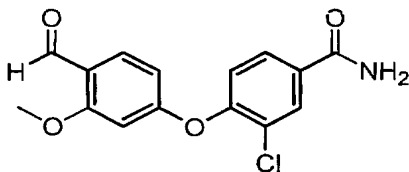
442



Preparation using a method similar to Example 703, step 1 yields the product (1.83 g, 94%).  $^1\text{H}$  NMR (DMSO- $d_6$ ) 10.24 (s, 1H), 8.26 (s, 1H), 7.87 (dd,  $J$  = 2.0 Hz, 8.5 Hz, 1H), 7.72 (d,  $J$  = 8.5 Hz, 1H), 7.33 (d,  $J$  = 8.5 Hz, 1H), 6.98 (d,  $J$  = 2.0 Hz, 1H), 6.61 (d,  $J$  = 8.5 Hz, 1H), 3.88 (s, 3H).

Step2:

3-Chloro-4-(4-formyl-3-methoxyphenoxy)-benzamide



Preparation using a method similar to Example 703, step 2 yields the product (1.73 g, 89%).  $^1\text{H}$  NMR (DMSO- $d_6$ ) 10.22 (s, 1H), 8.11 (d,  $J$  = 1.9 Hz, 1H), 8.1 (bs, 1H), 7.90 (dd,  $J$  = 1.9 Hz, 8.5 Hz, 1H), 7.70 (d,  $J$  = 8.7 Hz, 1H), 7.54 (bs, 1H), 7.32 (d,  $J$  = 8.5 Hz, 1H), 6.91 (d,  $J$  = 2.0 Hz, 1H), 6.49 (dd,  $J$  = 2.0 Hz, 8.7 Hz, 1H), 3.88 (s, 3H).

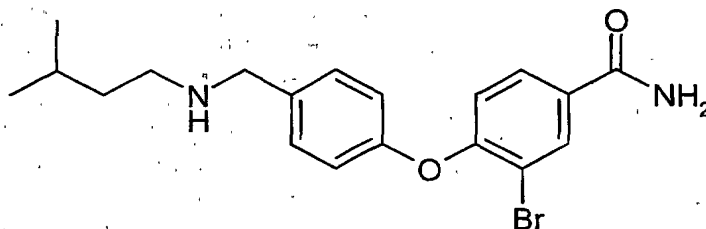
Step 3

Reductive amination of the compound of step 2 with n-pentylamine affords the title product (0.18 g, 86%). Mass spectrum (ion spray):  $m/z$  = 377.2 ( $M+1$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.93 (d,  $J$  = 2.0 Hz, 1H), 7.61 (dd,  $J$  = 2.1 Hz, 8.7 Hz, 1H), 7.20 (d,  $J$  = 8.2 Hz, 1H), 6.89 (d,  $J$  = 8.7 Hz, 1H), 6.59 (d,  $J$  = 2.1 Hz, 1H), 6.51 (dd,  $J$  = 2.1 Hz, 8.2 Hz, 1H), 6.33 (bs, 1H), 6.17 (bs, 1H), 3.78 (s, 3H), 3.74 (s, 2H), 2.59 (t,  $J$  = 7.2 Hz, 2H), 1.54-1.46 (m, 2H), 1.33-1.25 (m, 4H), 0.89 (t,  $J$  = 6.8 Hz, 3H).

### Example 708

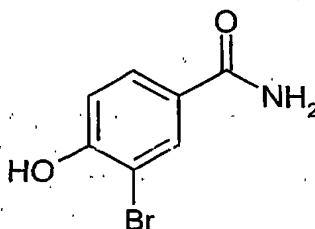
3-Bromo-4-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide )

443



## Step 1

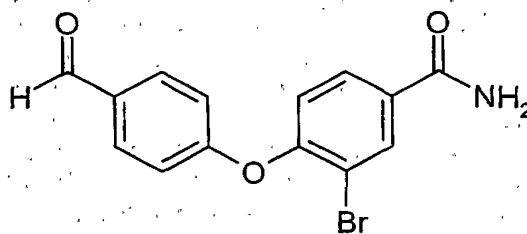
## 3-Bromo-4-hydroxy-benzamide



3-Bromo-4-hydroxy-benzonitrile (495 mg, 2.5 mmol) is dissolved in  $\text{H}_2\text{SO}_4$  98%, heat the solution at  $80^\circ\text{C}$  for 1 hour. Cool the mixture at room temperature and pour it into ice-water. Extract the aqueous layer with EtOAc. Dry the organic layer over  $\text{Na}_2\text{SO}_4$ . Eliminate the solvent to obtain the title compound (450 mg, 83%).  $^1\text{H-NMR}$  (methanol- $d_4$ , 200 MHz): 8.04 (d, 1H,  $J = 2.0$  Hz), 7.70 (dd, 1H,  $J = 2.0$  and 8.4 Hz), 6.93 (d, 1H,  $J = 8.6$  Hz)

## Step 2

## 3-Bromo-4-(4-formyl-phenoxy)-benzamide



Add  $\text{K}_2\text{CO}_3$  (1.49g, 10.8 mmol) to a solution of 4-fluorobenzaldehyde (1.16 mL, 10.8 mmol) and 3-bromo-4-hydroxy-benzamide (1.16g, 5.4 mmol) in DMF (20 mL). Heat the mixture under  $\text{N}_2$  overnight. Cool the mixture at room temperature and pour it into ice-water. Extract the aqueous layer with EtOAc. Dry the organic layer over  $\text{Na}_2\text{SO}_4$ . Eliminate the solvent. Purify by flash chromatography (eluent: EtOAc/hexane 2/1 and

4/1) to get the title compound (1.0g, 58%).  $^1\text{H-NMR}$  (methanol- $d_4$ , 300 MHz): 9.84 (s, 1H), 8.18 (d, 1H,  $J = 2.0$  Hz), 7.88-7.83 (m, 3H), 7.13 (d, 1H,  $J = 8.5$  Hz), 7.04-7.01 (m, 2H).

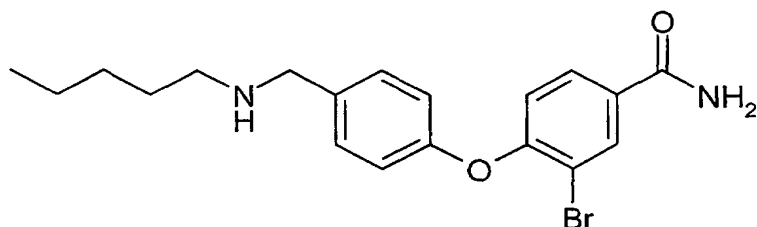
### Step 3

Reductive amination using the aldehyde obtained in the previous step following general procedures described previously afforded the desired compound.

Electrospray MS  $M+1$  ion = 391.  $^1\text{H-NMR}$  (methanol- $d_4$ , 300 MHz): 8.13 (d, 1H,  $J = 2.4$  Hz), 7.73 (dd, 1H,  $J = 2.0$  and 8.5 Hz), 7.33-7.31 (m, 2H), 6.93-6.90 (m, 2H), 6.83 (d, 1H,  $J = 8.5$  Hz), 3.69 (s, 2H), 2.57-2.51 (m, 2H), 1.61-1.30 (m, 3H), 0.83 (d, 6H,  $J = 6.4$  Hz).

### Example 709

3-Bromo-4-(3-pentylaminomethyl-phenoxy)-benzamide

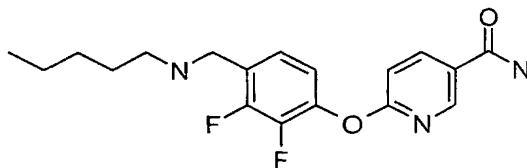


Using *n*-pentylbromide and following procedures similar to that of Example 707 afforded the title compound.

Electrospray MS  $M+1$  ion = 391.  $^1\text{H-NMR}$  (methanol- $d_4$ , 300 MHz): 8.12 (d, 1H,  $J = 2.0$  Hz), 7.73 (dd, 1H,  $J = 2.0$  and 8.5 Hz), 7.33-7.30 (m, 2H), 6.93-6.90 (m, 2H), 6.83 (d, 1H,  $J = 8.5$  Hz), 3.69 (s, 2H), 2.54-2.49 (m, 2H), 1.52-1.23 (m, 6H), 0.84 (t, 3H,  $J = 6.4$  Hz).

### Example 710

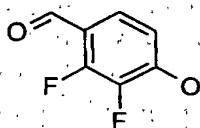
6-(2,3-Difluoro-4-pentylaminomethyl-phenoxy)-nicotinamide.



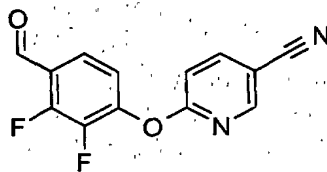
Step 1



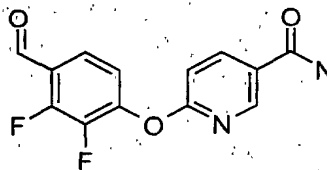
445

**2,3-Difluoro-4-hydroxy-benzaldehyde.**

Combine 2,3-difluoro-4-methoxy-benzaldehyde (2.76 g, 16.0 mmol) and pyridine hydrochloride (18.5 g, 160 mmol) in a round bottom flask equipped with nitrogen inlet. Heat the mixture at 170°C two hours, cool to near ambient temperature and dilute with water. Extract aqueous with EtOAc (2x), wash extract with 0.1 N aq. HCl (2x), water (2x) and brine, dry (MgSO<sub>4</sub>) and concentrate. Purify on silica gel (20% EtOAc / Hexane) to give 2,3-difluoro-4-hydroxy-benzaldehyde (1.71 g) as a yellow solid. <sup>1</sup>HNMR (CDCl<sub>3</sub>): 10.18 (s, 1H), 7.59 (t, 1H), 6.90 (t, 1H), 6.14 (s, 1H).

**Step 2****6-(2,3-Difluoro-4-formyl-phenoxy)-nicotinonitrile.**

Combine 2,3-difluoro-4-hydroxy-benzaldehyde (see Canadian patent 1190093) (1.93 g, 12.2 mmol), 6-chloronicotinonitrile (1.69 g, 12.2 mmol), K<sub>2</sub>CO<sub>3</sub> (2.53 g, 18.3 mmol) and DMA (30 ml) in a sealed, pressure vessel. Heat the suspension at 180°C for five minutes in a microwave (600 Watts), cool to near ambient temperature and pour into aqueous NH<sub>4</sub>Cl. Extract aqueous with EtOAc (2x), wash with water (2x) and brine, dry (MgSO<sub>4</sub>) and concentrate. Purify on silica gel (20% EtOAc / Hexane) to give 6-(2,3-difluoro-4-formyl-phenoxy)-nicotinonitrile (2.07 g) as a white solid. <sup>1</sup>HNMR (CDCl<sub>3</sub>): 10.33 (s, 1H), 8.42 (s, 1H), 8.02 (d, 1H), 7.73 (t, 1H), 7.20 (d, 1H), 7.15 (t, 1H).

**Step 3****6-(2,3-Difluoro-4-formyl-phenoxy)-nicotinamide.**

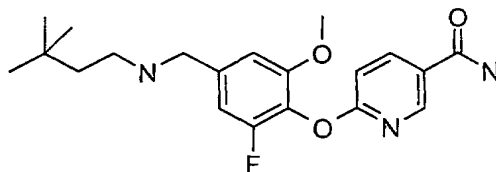
Add 30% aq.  $\text{H}_2\text{O}_2$  (7.95 ml) to a suspension of 6-(2,3-difluoro-4-formyl-phenoxy)-nicotinonitrile (2.07 g, 7.95 mmol),  $\text{K}_2\text{CO}_3$  (550 mg, 3.98 mmol) and DMSO (20 ml) stirring in an ice / water bath. After one hour, pour the reaction mixture into water and extract with EtOAc. Wash the extract with water and brine before drying ( $\text{MgSO}_4$ ) and concentrating to give 6-(2,3-difluoro-4-formyl-phenoxy)-nicotinamide (1.64 g) as a white solid.  $^1\text{H}$ NMR ( $\text{DMSO-d}_6$ ): 10.14 (s, 1H), 8.58 (s, 1H), 8.33 (d, 1H), 8.07 (s, 1H), 7.74 (t, 1H), 7.55 (s, 1H), 7.33 (d, 1H), 7.27 (t, 1H).

#### Step 4

Combine 6-(2,3-difluoro-4-formyl-phenoxy)-nicotinamide (278 mg, 1.00 mmol), n-pentylamine (105 mg, 1.20 mmol), and MeOH (3 ml) in a round bottom flask equipped with nitrogen inlet and stir for two hours. Add  $\text{NaBH}_4$  (57 mg, 1.50 mmol) and stir for an additional two hours before concentrating. Dissolve concentrate in EtOAc and wash with 5% aq. KOH and brine, dry ( $\text{Na}_2\text{SO}_4$ ), and concentrate. Purify on silica gel (5% (1 M  $\text{NH}_3$  / MeOH) / DCM) to give the title compound (290 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 350$  (M+1);  $^1\text{H}$ NMR ( $\text{DMSO-d}_6$ ): 8.55 (s, 1H), 8.28 (d, 1H), 8.03 (s, 1H), 7.50 (s, 1H), 7.29 (m, 1H), 7.22 (d, 1H), 7.15 (m, 1H), 3.73 (s, 2H), 2.48 (t, 2H), 1.41 (m, 2H), 1.25 (m, 4H), 0.84 (m, 3H).

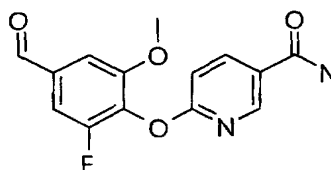
#### Example 711

6-{4-[(3,3-Dimethyl-butylamino)-methyl]-2-fluoro-6-methoxy-phenoxy}-nicotinamide



#### Step 1

6-(2-Fluoro-4-formyl-6-methoxy-phenoxy)-nicotinamide.



Using a method similar to Example 710, Step 2, using 3-fluoro-4-hydroxy-5-methoxy-benzaldehyde (Journal of Organic Chemistry (1986), 51(21), 4072-3.) (2.84 g, 16.7 mmol), 6-chloronicotinonitrile (2.31 g, 16.7 mmol) and  $K_2CO_3$  (3.46 g, 25.0 mmol) gives 6-(2-fluoro-4-formyl-6-methoxy-phenoxy)-nicotinonitrile (3.04 g) as a white solid.  $^1H$ NMR ( $CDCl_3$ ): 9.94 (s, 1H), 8.37 (s, 1H), 7.98 (d, 1H), 7.36 (m, 2H), 7.20 (d, 1H), 3.87 (s, 3H).

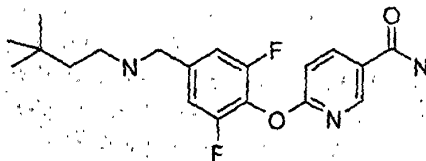
Hydrolysis of 6-(2-fluoro-4-formyl-6-methoxy-phenoxy)-nicotinonitrile (3.04 g, 11.1 mmol) in a similar manner as described for Example 710, Step 3, gives 6-(2-fluoro-4-formyl-6-methoxy-phenoxy)-nicotinamide (2.75 g) as a white solid.  $^1H$ NMR ( $DMSO-d_6$ ): 9.96 (s, 1H), 8.50 (s, 1H), 8.28 (d, 1H), 8.01 (s, 1H), 7.55 (m, 2H), 7.48 (s, 1H), 7.26 (d, 1H), 3.82 (s, 3H).

#### Step 2

Using a method similar to Example 710, Step 4, using 6-(2-fluoro-4-formyl-6-methoxy-phenoxy)-nicotinamide (250 mg, 0.861 mmol), 3,3-dimethyl-butylamine (104 mg, 1.03 mmol), and  $NaBH_4$  (49 mg, 1.29 mmol) gave the title compound (259 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 376$  (M+1):  $^1H$ NMR ( $DMSO-d_6$ ): 8.50 (s, 1H), 8.23 (d, 1H), 7.98 (s, 1H), 7.44 (s, 1H), 7.13 (d, 1H), 6.96 (s, 1H), 6.89 (d, 1H), 3.71 (s, 3H), 3.68 (s, 2H), 2.51 (t, 2H), 1.37 (t, 2H), 0.86 (s, 9H).

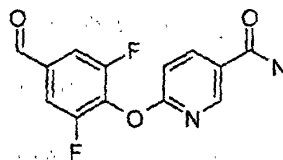
#### Example 712

6-{4-[(3,3-Dimethyl-butylamino)-methyl]-2,6-difluoro-phenoxy}-nicotinamide.



#### Step 1

6-(2,6-Difluoro-4-formyl-phenoxy)-nicotinamide.



Using a method similar to Example 710, Step 2, using 3,5-difluoro-4-hydroxy-benzaldehyde (Journal of Medicinal Chemistry (1989), 32(2), 450-5.) (2.50 g, 15.8 mmol), 6-chloronicotinonitrile (2.19 g, 15.8 mmol) and  $K_2CO_3$  (3.27 g, 23.7 mmol) gives 6-(4-formyl-2,6-difluoro-phenoxy)-nicotinonitrile (2.84 g) as a white solid.  $^1H$ NMR ( $CDCl_3$ ): 9.95 (s, 1H), 8.39 (s, 1H), 8.02 (d, 1H), 7.58 (d, 2H), 7.25 (d, 1H).

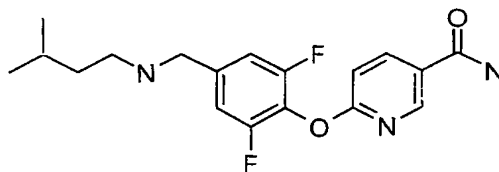
Hydrolysis of 6-(4-formyl-2,6-difluoro-phenoxy)-nicotinonitrile (3.47 g, 13.3 mmol) in a similar manner as described for Example 710, Step 3, gives 6-(2,6-difluoro-4-formyl-phenoxy)-nicotinamide (2.87 g) as a white solid.  $^1H$ NMR ( $CDCl_3$ ): 9.94 (s, 1H), 8.49 (s, 1H), 8.25 (d, 1H), 7.57 (d, 2H), 7.20 (d, 1H), 5.85 (br. s, 2H).

#### Step 2

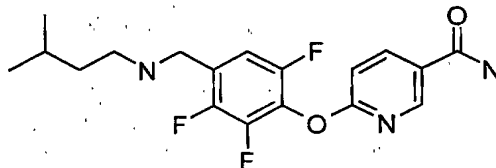
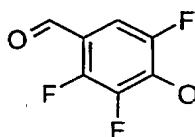
Using a method similar to Example 710, Step 4, using 6-(2,6-difluoro-4-formyl-phenoxy)-nicotinamide (278 mg, 1.00 mmol), 3,3-dimethylbutylamine (105 mg, 1.20 mmol), and  $NaBH_4$  (57 mg, 1.50 mmol) gave the title compound (292 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 364$  ( $M+1$ );  $^1H$ NMR ( $DMSO-d_6$ ): 8.54 (s, 1H), 8.30 (d, 1H), 8.04 (s, 1H), 7.51 (s, 1H), 7.29 (d, 1H), 7.22 (d, 2H), 3.71 (s, 2H), 2.49 (t, 2H), 1.36 (m, 2H), 0.86 (s, 9H).

#### Example 713

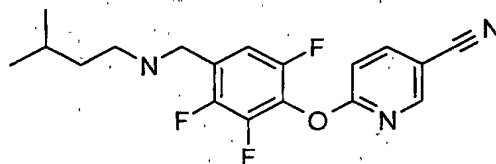
6-{2,6-Difluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide.



Using a method similar to Example 712, using 6-(2,6-difluoro-4-formyl-phenoxy)-nicotinamide (Example 712, Step 1) (139 mg, 0.500 mmol), isoamylamine (52 mg, 0.600 mmol), and  $NaBH_4$  (28 mg, 0.750 mmol) gave the title compound (148 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 350$  ( $M+1$ );  $^1H$ NMR ( $CDCl_3$ ): 8.51 (s, 1H), 8.21 (d, 1H), 7.14 (d, 1H), 7.03 (d, 2H), 5.74 (br. s, 2H), 3.79 (s, 2H), 2.65 (t, 2H), 1.66 (m, 1H), 1.41 (m, 2H), 0.91 (d, 6H).

**Example 714****6-{2,3,6-Trifluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide.****Step 1****2,3,5-Trifluoro-4-hydroxy-benzaldehyde.**

Add hexamethylenetetramine (7.10 g, 50.6 mmol) portion wise to a solution of 2,3,6-trifluorophenol (5.00 g, 33.7 mmol) in TFA (35 ml) at ambient temperature and reflux for 15 hours. After cooling, treat the reaction mixture with water (60 ml), followed by 50% aq. H<sub>2</sub>SO<sub>4</sub> (30 ml), and stir at ambient temperature for 30 minutes. Extract with EtOAc (2x) and wash with 1N aq. HCl (3x) and water. Extract the organic with 2N aq. NaOH (2x) and acidify the alkaline extract with conc. HCl while cooling in an ice / water bath. Collect the resulting solid via filtration and dry to give 2,3,5-trifluoro-4-hydroxy-benzaldehyde (2.97 g) as an off-white solid.

**Step 2****6-{2,3,6-Trifluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinonitrile.**

Using a method similar to Example 710, Part 2, using 2,3,5-trifluoro-4-hydroxy-benzaldehyde (1.00 g, 5.64 mmol), 6-chloronicotinonitrile (782 mg, 5.64 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.17 g, 8.47 mmol) gives 6-(2,3,6-trifluoro-4-formyl-phenoxy)-nicotinonitrile (907 mg) contaminated with 6-chloronicotinonitrile starting material. Dissolve this

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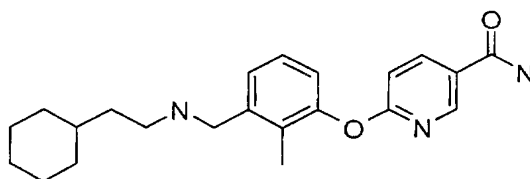
mixture in MeOH (15 ml) and treat with isoamylamine (194 mg, 2.23 mmol). After stirring for two hours, add NaBH<sub>4</sub> (105 mg, 2.79 mmol) and stir for an additional hour. Purification as described in Example 710, Step 4, gives 6-{2,3,6-trifluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinonitrile (383 mg) as a colorless oil.

### Step 3

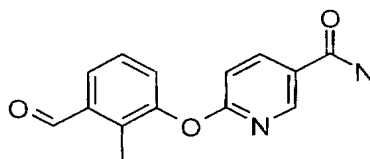
Hydrolysis of 6-{2,3,6-trifluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinonitrile (383 mg, 1.09 mmol) in a similar manner as described for Example 710, Step 3, gives the title compound (374 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 368$  (M+1); <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.50 (s, 1H), 8.23 (d, 1H), 7.16 (d, 1H), 7.08 (m, 1H), 5.83 (br. s, 2H), 3.87 (s, 2H), 2.66 (t, 2H), 1.64 (m, 1H), 1.41 (m, 2H), 0.90 (d, 6H).

### Example 715

6-{3-[(2-Cyclohexyl-ethylamino)-methyl]-2-methyl-phenoxy}-nicotinamide.



### Step 1



6-(3-Formyl-2-methyl-phenoxy)-nicotinamide.

Using a method similar to Example 221, Step 1, using 2-methyl-3-hydroxy-benzaldehyde (see European Patent 0807621 A1) (965 mg, 6.42 mmol), 6-chloronicotinonitrile (890 mg, 6.42 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.33 g, 9.63 mmol) gives 6-(3-formyl-2-methyl-phenoxy)-nicotinonitrile (1.40 g) as a white solid. <sup>1</sup>HNMR (CDCl<sub>3</sub>): 10.30 (s, 1H), 8.41 (s, 1H), 7.96 (d, 1H), 7.78 (d, 1H), 7.45 (t, 1H), 7.30 (d, 1H), 7.10 (d, 1H), 2.45 (s, 3H).

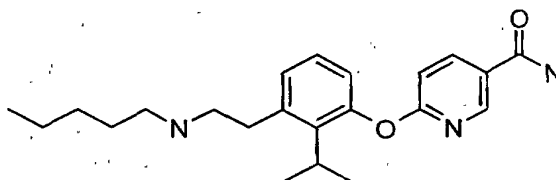
Hydrolysis of 6-(3-formyl-2-methyl-phenoxy)-nicotinonitrile (1.40 g, 5.55 mmol) in a similar manner as described for Example 710, Step 3, gives 6-(3-formyl-2-methyl-phenoxy)-nicotinamide (1.27 g) as a white solid. <sup>1</sup>HNMR (CDCl<sub>3</sub>): 10.31 (s, 1H), 8.52 (s, 1H), 8.21 (d, 1H), 7.76 (d, 1H), 7.44 (t, 1H), 7.32 (d, 1H), 7.04 (d, 1H), 5.77 (br. s, 2H), 2.47 (s, 3H).

#### Step 2

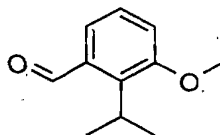
Using a method similar to Example 710, Step 4, using 6-(3-formyl-2-methyl-phenoxy)-nicotinamide (256 mg, 1.00 mmol), cyclohexylethylamine (Synthesis (1983), (5), 388-9) (190 mg, 1.50 mmol), and NaBH<sub>4</sub> (57 mg, 1.50 mmol) gave the title compound (325 mg) as a white solid. Mass spectrum (ion spray): m/z = 368 (M+1); <sup>1</sup>HNMR (DMSO-d<sub>6</sub>): 8.54 (s, 1H), 8.21 (d, 1H), 7.98 (s, 1H), 7.43 (s, 1H), 7.22-7.14 (m, 2H), 7.00 (d, 1H), 6.92 (d, 1H), 3.65 (s, 2H), 2.53 (t, 2H), 2.00 (s, 3H), 1.66-1.55 (m, 5H), 1.35-1.27 (m, 3H), 1.20-1.06 (m, 3H), 0.84 (m, 2H).

#### Example 716

##### 6-[2-Isopropyl-3-(2-pentylamino-ethyl)-phenoxy]-nicotinamide.



#### Step 1



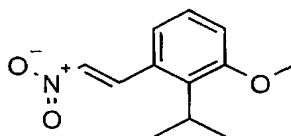
##### 2-Isopropyl-3-methoxy-benzaldehyde.

Add drop wise a 1 M DIBAL-H /toluene solution (122 mmol) over two hours, to a solution of 2-isopropyl-3-methoxy-benzonitrile (see JCS 13, 489, (1948)), (10.7 g, 61.0 mmol) in toluene (200 ml), stirring under nitrogen at -78°C. After the

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addition is complete, allow the reaction mixture to warm to 0°C over two hours and maintain at 0°C for an additional two hours. Quench the reaction mixture by drop wise addition of AcOH (35 ml), followed by water (100 ml), and stir at ambient temperature for two hours. Dilute with additional water (100 ml), separate layers, extract aqueous with EtOAc (2x), and wash combined organic with water (2x) and brine. After drying (Na<sub>2</sub>SO<sub>4</sub>) and concentrating, purify crude on silica gel (10% EtOAc / hexane) to give 2-isopropyl-3-methoxy-benzaldehyde (8.81 g) as a yellow oil. <sup>1</sup>HNMR (CDCl<sub>3</sub>): 10.45 (s, 1H), 7.42 (d, 1H), 7.27 (t, 1H), 7.07 (d, 1H), 4.03 (m, 1H), 3.85 (s, 3H), 1.39 (d, 6H).

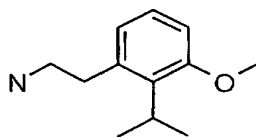
## Step 2



2-Isopropyl-1-methoxy-3-(2-nitro-vinyl)-benzene.

Using a method similar to Example 659, Step 1, using 2-isopropyl-3-methoxy-benzaldehyde (3.56 g, 20.0 mmol), nitromethane (3.25 ml, 60.0 mmol), ammonium acetate (2.00 g, 26.0 mmol) and acetic acid (25 ml) gave 2-isopropyl-1-methoxy-3-(2-nitro-vinyl)-benzene (3.92 g) as a viscous oil. <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.48 (d, 1H), 7.38 (d, 1H), 7.20 (t, 1H), 7.02-6.96 (m, 2H), 3.84 (s, 3H), 3.41 (m, 1H), 1.36 (d, 6H).

## Step 3



2-(2-Isopropyl-3-methoxy-phenyl)-ethylamine.

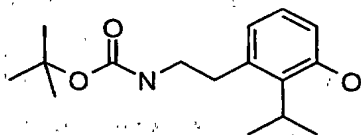
Using a method similar to Example 659, Step 2, using 2-isopropyl-1-methoxy-3-(2-nitro-vinyl)-benzene (3.92 g, 17.7 mmol), LAH (53.1 mmol) and AlCl<sub>3</sub> (53.1 mmol) gave 2-(2-isopropyl-3-methoxy-phenyl)-ethylamine (3.4 g) as a viscous oil. <sup>1</sup>HNMR (CDCl<sub>3</sub>): 7.08 (t, 1H), 6.77-6.73 (m, 2H), 3.80 (s, 3H), 3.22 (m, 1H), 2.89 (m, 2H), 2.80 (m, 2H), 1.32 (d, 6H).



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## Step 4

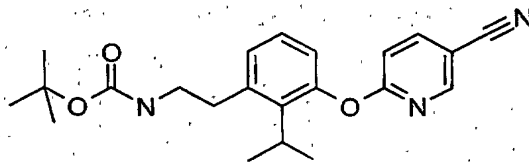
[2-(3-Hydroxy-2-isopropyl-phenyl)-ethyl]-carbamic acid tert-butyl ester.



Add 1M BBr<sub>3</sub> / DCM (44.2 mmol) drop wise, over 40 minutes, to a solution of 2-(2-isopropyl-3-methoxy-phenyl)-ethylamine (3.4 g, 17.7 mmol) in DCM (40 ml) stirring at -78°C under nitrogen. After addition is complete, stir at ambient temperature for two hours. Cool reaction mixture back to -78°C, quench with MeOH (25 ml) and concentrate. To this crude material, add THF (50 ml), 1M aq. K<sub>2</sub>CO<sub>3</sub> (45 ml) and Boc<sub>2</sub>O (4.24 g, 19.4 mmol), and stir overnight at ambient temperature. After pouring the reaction mixture into aq. NH<sub>4</sub>Cl, extract with EtOAc, wash extract with brine, dry (Na<sub>2</sub>SO<sub>4</sub>) and concentrate. Purify crude on silica gel (10% to 40% EtOAc / hexane) to give [2-(3-hydroxy-2-isopropyl-phenyl)-ethyl]-carbamic acid tert-butyl ester (4.02 g) as a viscous, amber oil. <sup>1</sup>HNMR (CDCl<sub>3</sub>): 6.97 (t, 1H), 6.70 (d, 1H), 6.58 (d, 1H), 4.58 (br. s, 1H), 3.30 (m, 2H), 3.23 (m, 1H), 2.83 (t, 2H), 1.44 (s, 9H), 1.37 (d, 6H).

## Step 5

{2-[3-(5-Cyano-pyridin-2-yloxy)-2-isopropyl phenyl]-ethyl}-carbamic acid tert-butyl ester.



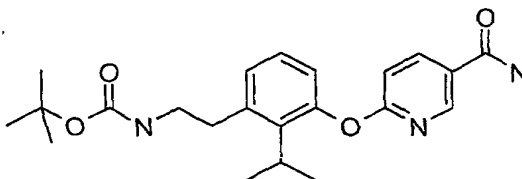
Using a method similar to Example 221, Step 1, using [2-(3-hydroxy-2-isopropyl-phenyl)-ethyl]-carbamic acid tert-butyl ester (4.02 g, 14.4 mmol), 6-chloronicotino-nitrile (1.99 g, 14.4 mmol) and K<sub>2</sub>CO<sub>3</sub> (2.98 g, 21.5 mmol) gives {2-[3-(5-cyano-pyridin-2-yloxy)-2-isopropyl-phenyl]-ethyl}-carbamic acid tert-butyl ester (4.11 g) as a yellow foam. <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.50 (s, 1H), 7.92 (d, 1H), 7.17 (t, 1H), 7.06 (d, 1H), 7.01 (d,

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1H), 6.86 (d, 1H), 4.63 (br. s, 1H), 3.34 (m, 2H), 3.27 (m, 1H), 2.91 (t, 2H), 1.44 (s, 9H), 1.24 (d, 6H).

## Step 6

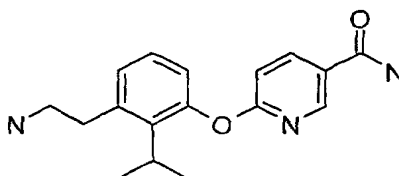
{2-[3-(5-Carbamoyl-pyridin-2-yloxy)-2-isopropyl-phenyl]-ethyl}-carbamic acid tert-butyl ester.



Hydrolysis of {2-[3-(5-cyano-pyridin-2-yloxy)-2-isopropyl-phenyl]-ethyl}-carbamic acid tert-butyl ester (4.11 g, 10.7 mmol) in a similar manner as described for Example 710, Step 3, gives {2-[3-(5-Carbamoyl-pyridin-2-yloxy)-2-isopropyl-phenyl]-ethyl}-carbamic acid tert-butyl ester (4.30 g) as a yellow foam. <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.63 (s, 1H), 8.18 (d, 1H), 7.15 (t, 1H), 7.03 (d, 1H), 6.95 (d, 1H), 6.86 (d, 1H), 5.98 (br. s, 2H), 4.67 (br. s, 1H), 3.34 (m, 2H), 3.26 (m, 1H), 2.90 (t, 2H), 1.44 (s, 9H), 1.26 (d, 6H).

## Step 7

6-[3-(2-Amino-ethyl)-2-isopropyl-phenoxy]-nicotinamide.



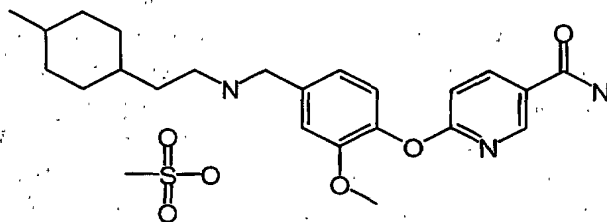
Deprotection of {2-[3-(5-Carbamoyl-pyridin-2-yloxy)-2-isopropyl-phenyl]-ethyl}-carbamic acid tert-butyl ester (4.30 g, 10.7 mmol) as described in Example 651, Step 6, gave 6-[3-(2-amino-ethyl)-2-isopropyl-phenoxy]-nicotinamide (2.72 g) as a white foam. <sup>1</sup>HNMR (DMSO-d<sub>6</sub>): 8.59 (s, 1H), 8.23 (d, 1H), 8.01 (s, 1H), 7.44 (s, 1H), 7.11 (t, 1H), 7.03-6.98 (m, 2H), 6.80 (d, 1H), 3.24 (m, 1H), 2.71 (m, 4H), 1.72 (br. s, 2H), 1.17 (d, 6H).

## Step 8

Using a method similar to Example 710, Step 4, using 6-[3-(2-amino-ethyl)-2-isopropyl-phenoxy]-nicotinamide (299 mg, 1.00 mmol), valeraldehyde (112 mg, 1.30 mmol), and  $\text{NaBH}_4$  (57 mg, 1.50 mmol) gave the title compound (245 mg) as a colorless glass. Mass spectrum (ion spray):  $m/z = 370$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ): 8.59 (s, 1H), 8.22 (d, 1H), 8.00 (s, 1H), 7.44 (s, 1H), 7.10 (t, 1H), 7.01 (m, 2H), 6.80 (d, 1H), 3.24 (m, 1H), 2.76 (m, 2H), 2.63 (m, 2H), 2.50 (m, 2H), 1.38 (m, 2H), 1.25 (m, 4H), 1.16 (d, 6H), 0.84 (t, 3H).

### Example 717

6-(2-Methoxy-4-[[2-(4-methylcyclohexyl)ethylamino]methyl}phenoxy)nicotinamide



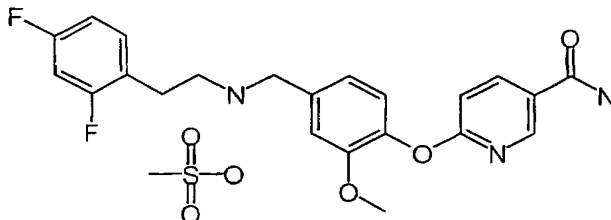
methanesulfonate

Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.100 g, 0.367 mmol), 2-(4-methylcyclohexyl)ethylamine (0.0571 g, 0.404 mmol) and 3 Å molecular sieves in a vial. Add methanol (3.6 mL), cap and stir overnight. Add  $\text{NaBH}_4$  (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 5 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 10 g ISCO® column with 6% to 15% (2.0 M  $\text{NH}_3$  in methanol) in ethyl acetate to give 6-(2-methoxy-4-[[2-(4-methylcyclohexyl)ethylamino]methyl}phenoxy)nicotinamide (0.0958 g, 65.6%).

Dissolve the compound in dichloromethane (2.5 mL) and add 1 equivalent of 0.50 M methanesulfonic acid in dichloromethane. Stir the solution for a short time before concentrating to afford the title compound: TOF MS  $\text{ES}^+$  398.2 ( $M+H$ ) $^+$ , HRMS calcd for  $\text{C}_{23}\text{H}_{32}\text{N}_3\text{O}_3$  398.2444 ( $M+H$ ) $^+$ , found 398.2440, time 0.52 min; Anal. Calcd for  $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_3 \cdot 0.5\text{H}_2\text{O}$ : C, 57.35; H, 7.22; N, 8.36. Found: C, 57.33; H, 6.94; N, 8.34.

**Example 718**

6-(4-{{[2-(2,4-Difluorophenyl)ethylamino]methyl}-2-methoxyphenoxy}nicotinamide



methanesulfonate

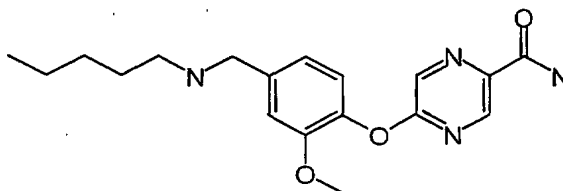
To a slurry of  $\text{LiAlH}_4$  (0.417 g, 11.0 mmol) in THF (25 mL), add  $\text{AlCl}_3$  (1.47 g, 11.0 mmol) in THF (10 mL). Cool the reaction mixture to  $0^\circ\text{C}$  and slowly add 2,4-difluorophenylacetonitrile (0.11 g, 6.53 mmol). Quench with saturated aqueous  $\text{Na}_2\text{CO}_3$  (10 mL) and filter through a Celite<sup>®</sup> pad. Dilute the filtrate to 150 mL with dichloromethane. Extract the product out with 1.0 N HCl (2 X 100 mL). Add 5.0 N NaOH to the aqueous layer until it is basic. Extract the aqueous layer with dichloromethane (2 X 100 mL), dry the organic layer over  $\text{Na}_2\text{SO}_4$ , filter and concentrate to afford the 2-(2,4-difluorophenyl)ethylamine as the crude amine.

Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.300 g, 1.10 mmol), 2-(2,4-difluorophenyl)ethylamine (0.343 g, 2.184 mmol) and 3 Å molecular sieves in a vial. Add methanol (4.4 mL), cap and stir overnight. Add  $\text{NaBH}_4$  (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 2% to 20% (2.0 M  $\text{NH}_3$  in methanol) in ethyl acetate to give 6-(4-{{[2-(2,4-difluorophenyl)ethylamino]methyl}-2-methoxyphenoxy}nicotinamide. Dissolve the compound in methanol (5.0 mL) and add 1 equivalent of 0.50 M methanesulfonic acid in dichloromethane. Stir the solution for a short time before concentrating to give the title compound: TOF MS  $\text{ES}^+$  414.2 ( $\text{M}+\text{H}^+$ ), HRMS calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_3\text{O}_3\text{F}_2$  414.1629 ( $\text{M}+\text{H}^+$ ), found 414.1613, time 0.52 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18 min],  $t_r$  = 11.6 min, 100% purity.

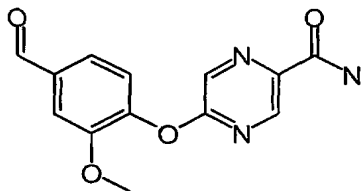
**Example 719**

5-(2-Methoxy-4-pentylaminomethylphenoxy)pyrazine-2-carboxamide

457



## Part A: 5-(4-Formyl-2-methoxyphenoxy)pyrazine-2-carboxamide



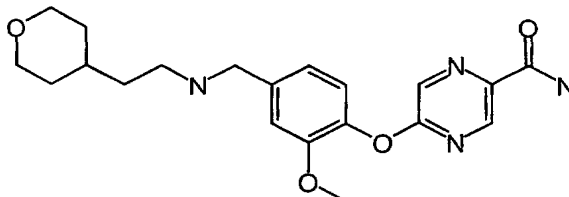
Dissolve 5-chloropyrazine-2-carboxamide (Example 387, Part A) (0.374 g, 2.34 mmol) and vanillin (0.361 g, 2.34 mmol) in DMF (23.7 mL). Add  $K_2CO_3$  (0.821 g, 8.94 mmol) and heat at 100 °C for 1.5 hours. Concentrate the reaction mixture. Take the solid up in water (50 mL) and extract with dichloromethane (3 X 100 mL). Dry the organic layer over  $Na_2SO_4$ , filter and concentrate to give the title compound (0.625 g, 96.4%): TOF MS  $ES^+$  274.1 (M+H) $^+$ , HRMS calcd for  $C_{13}H_{12}N_3O_4$  274.0828 (M+H) $^+$ , found 274.0829, time 0.55 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95 over 19 min],  $t_R$  = 10.2 min, 98.1% purity.

## Part B: 5-(2-Methoxy-4-pentylaminomethylphenoxy)pyrazine-2-carboxamide

Place 5-(4-formyl-2-methoxyphenoxy)pyrazine-2-carboxamide (Example 719, Part A) (0.200 g, 0.732 mmol), amylamine (0.0670 g, 0.769 mmol) and 3 Å molecular sieves in a vial. Add methanol (3.6 mL), cap and stir overnight. Add  $NaBH_4$  (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 60% to 90% (5% (2.0 M  $NH_3$  in methanol) in ethyl acetate) in hexanes. Concentrate the fractions containing the product. Take the solid up in ethyl acetate (50 mL) and wash with 1.0 N NaOH to give the title compound (0.180 g, 71.7%): TOF MS  $ES^+$  345.2 (M+H) $^+$ , HRMS calcd for  $C_{18}H_{25}N_4O_3$  345.1927 (M+H) $^+$ , found 345.1926, time 0.52 min; HPLC [Waters XTerra<sup>™</sup> C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 23 min],  $t_R$  = 10.4 min, 100% purity.

**Example 720**

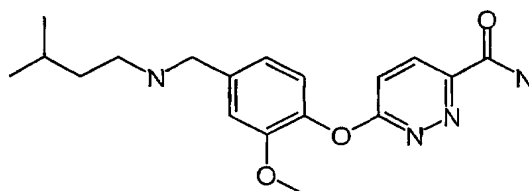
5-(2-Methoxy-4-{{2-(tetrahydropyran-4-yl)ethylamino}methyl}phenoxy)pyrazine-2-carboxamide



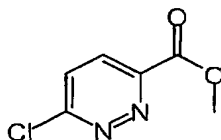
Place 5-(4-Formyl-2-methoxyphenoxy)pyrazine-2-carboxamide ( Example 719, Part A) (0.200 g, 0.732 mmol), 2-(tetrahydropyran-4-yl)ethylamine (0.0993 g, 0.769 mmol) and 3Å molecular sieves in a vial. Add methanol (3.6 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column 5% to 20% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate. Concentrate the fractions containing the product. Take the solid up in ethyl acetate (50 mL) and wash with 1.0 N NaOH to give the title compound (0.168 g, 59.4%): TOF MS ES<sup>+</sup> 387.2031 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>27</sub>N<sub>4</sub>O<sub>4</sub> 387.2032 (M+H)<sup>+</sup>, found 387.2031, time 0.52 min; HPLC [Waters XTerra™ C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 25 min], t<sub>R</sub> = 8.7 min, 100% purity.

**Example 721**

6-{2-Methoxy-4-[(3-methylbutylamino)methyl]phenoxy}pyridazine-3-carboxamide

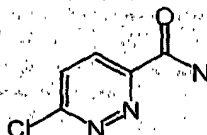


Part A: Methyl 6-chloropyridazine-3-carboxylate



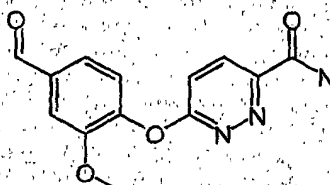
Dissolve 6-oxo-1,6-dihydropyridazine-3-carboxylic acid monohydrate (33.0 g, 209 mmol) in  $\text{SOCl}_2$  (700 mL) and reflux for 2.5 hours. Concentrate the dark solution to complete dryness. Take the solid up in dichloromethane (700 mL), cool to 0 °C and add methanol (9.6 mL) and triethylamine (54.5 mL). Allow the reaction mixture to warm to room temperature as it stirs overnight. Load the reaction mixture onto a silica gel plug. Wash the plug with 20% ethyl acetate in dichloromethane. Purify the impure fractions by chromatography eluting with 50% ethyl acetate in dichloromethane to give the title compound (29.4 g, 82%): TOF MS  $\text{ES}^+$  173.0 ( $\text{M}+\text{H}$ ) $^+$ ; HRMS calcd for  $\text{C}_6\text{H}_6\text{N}_2\text{O}_2\text{Cl}$  173.0118 ( $\text{M}+\text{H}$ ) $^+$ , found 173.0130, time 0.53 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18],  $t_R$  = 6.9 min, 100% purity.

Part B: 6-Chloropyridazine-3-carboxamide



Dissolve methyl 6-chloropyridazine-3-carboxylate (0.498 g, 2.89 mmol) in methanol (28 mL). Cool the solution to 0 °C with an acetone/dry ice bath. Bubble ammonia into the reaction mixture, then allow it to warm to 0 °C over 1 hour before concentrating to give the title compound (0.451 g, 99%): TOF MS  $\text{ES}^+$  157.0 ( $\text{M}$ ) $^+$ , HRMS calcd for  $\text{C}_5\text{H}_4\text{N}_3\text{OCl}$  157.0043 ( $\text{M}$ ) $^+$ , found 157.0010, time 4.45 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.1 TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 10-20% over 5 min then 20-95% over 18],  $t_R$  = 5.2 min, 100% purity.

Part C: 6-(4-Formyl-2-methoxyphenoxy)pyridazine-3-carboxamide



Dissolve 5-chloropyridazine-2-carboxamide (Example 721, Part B) (0.502 g, 3.18 mmol) and vanillin (0.484 g, 3.18 mmol) in DMF (16 mL). Add  $\text{K}_2\text{CO}_3$  (1.10 g, 7.96

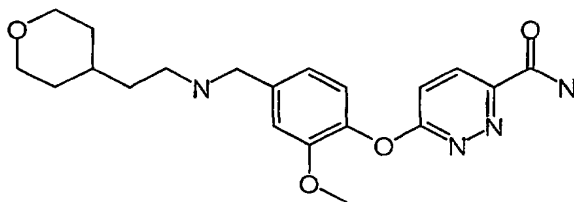
mmol) and heat at 100 °C for 3.6 hours. Concentrate the reaction mixture. Take the solid up in water (100 mL) and extract with dichloromethane (3 X 100 mL). Dry the organic layer over MgSO<sub>4</sub>, filter and concentrate to give the title compound (0.824 g, 95%): TOF MS ES<sup>+</sup> 274.1 (M+H)<sup>+</sup>, HRMS calcd for C<sub>13</sub>H<sub>12</sub>N<sub>3</sub>O<sub>4</sub> 274.0828 (M+H)<sup>+</sup>, found 274.0832, time 0.59 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95 over 19 min], t<sub>R</sub> = 11.4 min, 96.3% purity.

**Part D: 6-{2-Methoxy-4-[(3-methylbutylamino)methyl]phenoxy}pyridazine-3-carboxamide**

Place 6-(4-formyl-2-methoxyphenoxy)pyridazine-3-carboxamide ( Example 721, Part C) (0.200 g, 0.732 mmol), isoamylamine (0.0670 g, 0.769 mmol) and 3Å molecular sieves in a vial. Add methanol (3.6 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 10% to 20% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate. Concentrate the fractions containing the product. Take the solid up in ethyl acetate (50 mL) and wash with 1.0 N NaOH (2 X 10 mL). Dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate to give the title compound (0.112 g, 44%): TOF MS ES<sup>+</sup> 345.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>25</sub>N<sub>4</sub>O<sub>3</sub> 345.1927 (M+H)<sup>+</sup>, found 345.1926, time 0.52 min; Anal. Calcd for C<sub>18</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>: C, 62.77; H, 7.02; N, 16.27. Found: C, 62.29; H, 7.01; N, 15.50.

**Example 722**

**6-(2-Methoxy-4-{[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)pyridazine-3-carboxamide**

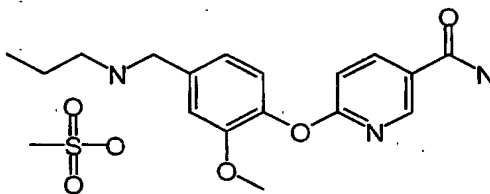




Place 6-(4-formyl-2-methoxyphenoxy)pyridazine-3-carboxamide (Example 721, Part C) (0.200 g, 0.732 mmol), 2-(tetrahydropyran-4-yl)ethylamine (0.0993 g, 0.769 mmol) and 3 Å molecular sieves in a vial. Add methanol (3.6 mL), cap and stir overnight. Add  $\text{NaBH}_4$  (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 10% to 20% (2.0 M  $\text{NH}_3$  in methanol) in ethyl acetate. Concentrate the fractions containing the product. Take the solid up in ethyl acetate (50 mL) and wash with 1.0 N  $\text{NaOH}$  (2 X 10 mL). Dry the organic layer over  $\text{Na}_2\text{SO}_4$ , filter and concentrate to give the title compound (0.154 g, 54%): TOF MS  $\text{ES}^+$  387.2 ( $\text{M}+\text{H}$ ) $^+$ , HRMS calcd for  $\text{C}_{20}\text{H}_{27}\text{N}_4\text{O}_4$  387.2032 ( $\text{M}+\text{H}$ ) $^+$ , found 387.2024, time 0.52 min; Anal. Calcd for  $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_4$ : C, 62.16; H, 6.78; N, 14.50. Found: C, 61.58; H, 6.66; N, 14.13.

#### Example 723

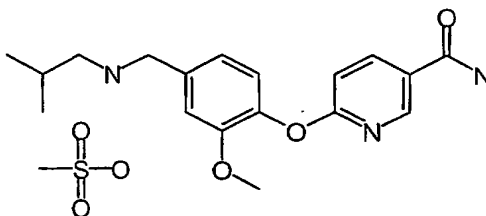
6-(2-Methoxy-4-propylaminomethylphenoxy)nicotinamide methanesulfonate



Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), propylamine (0.060 g, 1.01 mmol) and 3 Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add  $\text{NaBH}_4$  (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 5% to 15% (2.0 M  $\text{NH}_3$  in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.327 g, 84%): TOF MS  $\text{ES}^+$  316.2 ( $\text{M}+\text{H}$ ) $^+$ , HRMS calcd for  $\text{C}_{17}\text{H}_{22}\text{N}_3\text{O}_3$  316.1661 ( $\text{M}+\text{H}$ ) $^+$ , found 316.1671, time 0.52 min; HPLC [YMC-Pro Pack C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 10-20% over 5 min, then 20-95% over 18 min],  $t_R$  = 8.3 min, 100% purity.

**Example 724**

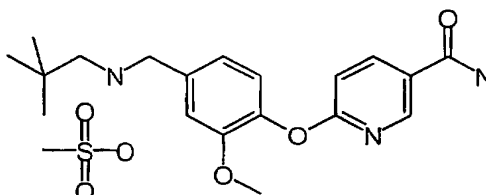
6-[4-(Isobutylaminomethyl)-2-methoxyphenoxy]nicotinamide methanesulfonate



Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), isobutylamine (0.074 g, 1.01 mmol) and 3Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 5% to 15% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.344 g, 87%): TOF MS ES<sup>+</sup> 330.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub> 330.1818 (M+H)<sup>+</sup>, found 330.1808, time 0.52 min; HPLC [YMC-Pro Pack C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 10-20% over 5 min, then 20-95% over 18 min], t<sub>R</sub> = 9.2 min, 100% purity.

**Example 725**

6-{4-[(2,2-Dimethylpropylamino)methyl]-2-methoxyphenoxy}nicotinamide methanesulfonate

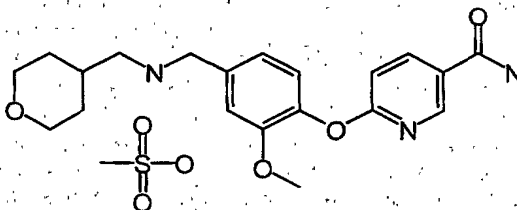


Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), neopentylamine (0.074 g, 1.01 mmol) and 3Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions)

and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 5% to 20% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to afford the title compound (0.339 g, 89%): TOF MS ES<sup>+</sup> 344.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub> 344.1974 (M+H)<sup>+</sup>, found 344.1963, time 0.52 min; HPLC [YMC-Pro Pack C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 10-20% over 5 min, then 20-95% over 18 min], t<sub>R</sub> = 9.9 min, 99.2% purity.

#### Example 726

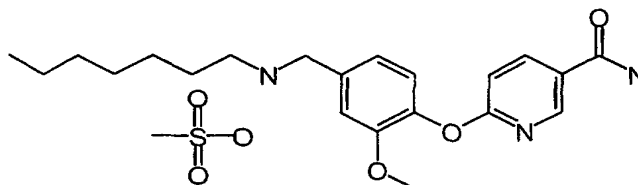
6-(2-Methoxy-4-{{(tetrahydropyran-4-ylmethyl)amino}methyl}phenoxy)nicotinamide methanesulfonate



Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), 4-aminomethyltetrahydropyran (0.116 g, 1.01 mmol) and 3Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 5% to 15% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.375 g, 85%): TOF MS ES<sup>+</sup> 372.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>26</sub>N<sub>3</sub>O<sub>4</sub> 372.1923 (M+H)<sup>+</sup>, found 372.1909, time 0.50 min; HPLC [YMC-Pro Pack C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 10-20% over 5 min, then 20-95% over 18 min], t<sub>R</sub> = 8.3 min, 100% purity.

**Example 727**

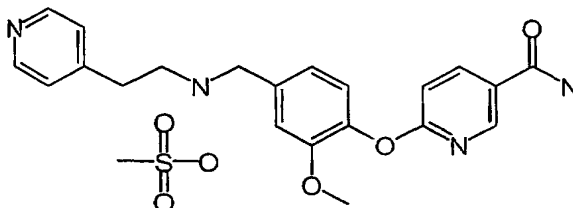
6-(4-Heptylaminomethyl-2-methoxyphenoxy)nicotinamide methanesulfonate



Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), heptylamine (0.060 g, 1.01 mmol) and 3Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 5% to 15% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.341 g, 79%): TOF MS ES<sup>+</sup> 372.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>30</sub>N<sub>3</sub>O<sub>3</sub> 372.2287 (M+H)<sup>+</sup>, found 372.2294, time 0.52 min; HPLC [YMC-Pro Pack C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 10-20% over 5 min, then 20-95% over 18 min], t<sub>R</sub> = 12.7 min, 99.0% purity.

**Example 728**

6-{2-Methoxy-4-[(2-pyridin-4-ylethylamino)methyl]phenoxy}nicotinamide methanesulfonate

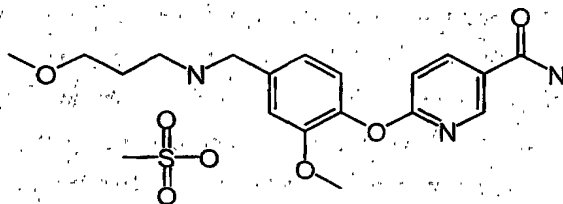


Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), 2-pyridin-4-ylethylamine (0.060 g, 1.01 mmol) and 3Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two

portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 5% to 25% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.339 g, 76%): TOF MS ES<sup>+</sup> 379.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>23</sub>N<sub>4</sub>O<sub>3</sub> 379.1770 (M+H)<sup>+</sup>, found 379.1753, time 0.32 min; IR (KBr) 3418 (N-H), 1194 (O-CH<sub>3</sub>), 1668 (C=O), 1610 (H<sub>2</sub>NCO-) cm<sup>-1</sup>.

### Example 729

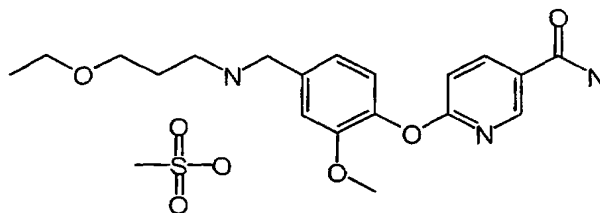
6-{2-Methoxy-4-[(3-methoxypropylamino)methyl]phenoxy}nicotinamide  
methanesulfonate



Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), 3-methoxypropylamine (0.090 g, 1.01 mmol) and 3Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 5% to 15% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.328 g, 82%): TOF MS ES<sup>+</sup> 346.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>24</sub>N<sub>3</sub>O<sub>4</sub> 346.1767 (M+H)<sup>+</sup>, found 346.1766, time 0.52 min; HPLC [Waters XTerra™ C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95 over 23 min], t<sub>R</sub> = 7.7 min, 100% purity.

### Example 730

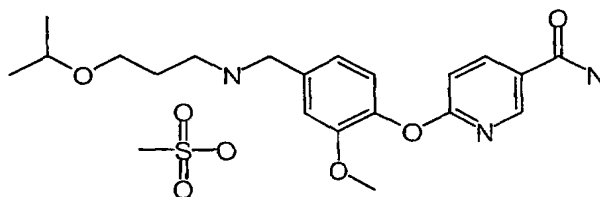
6-{4-[(3-Ethoxypropylamino)methyl]-2-methoxyphenoxy}nicotinamide  
methanesulfonate



Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), 3-ethoxypropylamine (0.060 g, 1.01 mmol) and 3 Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 5% to 15% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.325 g, 82%): TOF MS ES<sup>+</sup> 360.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>26</sub>N<sub>3</sub>O<sub>4</sub> 360.1923 (M+H)<sup>+</sup>, found 360.1920, time 0.52 min; HPLC [YMC-Pro Pack C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 10-20% over 5 min, then 20-95% over 18 min], t<sub>R</sub> = 9.3 min, 100% purity.

### Example 731

6-{4-[(3-Isopropoxypropylamino)methyl]-2-methoxyphenoxy}nicotinamide  
methanesulfonate

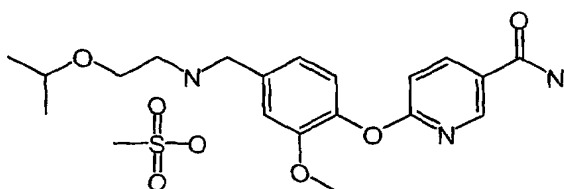


Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), 3-isopropoxypropylamine (0.060 g, 1.01 mmol) and 3 Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a

25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 5% to 15% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.353 g, 84%): TOF MS ES<sup>+</sup> 374.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>28</sub>N<sub>3</sub>O<sub>4</sub> 374.2080 (M+H)<sup>+</sup>, found 374.2080, time 0.52 min; HPLC [YMC-Pro Pack C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 10-20% over 5 min, then 20-95% over 18 min], t<sub>R</sub> = 10.1 min, 100% purity.

### Example 732

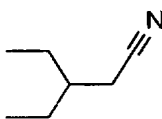
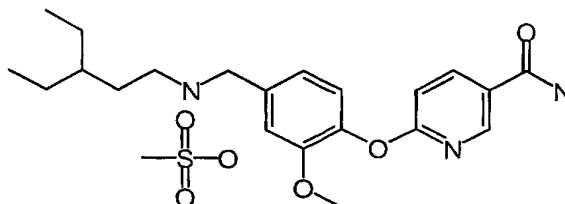
6-{4-[(2-Isopropoxyethylamino)methyl]-2-methoxyphenoxy}nicotinamide methanesulfonate



Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), 2-aminoethyl isopropyl ether (0.060 g, 1.01 mmol) and 3 Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 5% to 15% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.333 g, 81%): TOF MS ES<sup>+</sup> 360.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>26</sub>N<sub>3</sub>O<sub>4</sub> 360.1923 (M+H)<sup>+</sup>, found 360.1939, time 0.52 min; HPLC [YMC-Pro Pack C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 10-20% over 5 min, then 20-95% over 18 min], t<sub>R</sub> = 9.7 min, 99.2% purity.

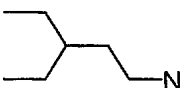
**Example 733**

6-{4-[(3-Ethylpentylamino)methyl]-2-methoxyphenoxy}nicotinamide methanesulfonate



Part A: 3-Ethylpentanenitrile

To a suspension of sodium cyanide (3.33 g, 67.8 mmol) in DMSO (24 mL) at 60 °C, slowly add 1-bromo-2-ethylbutane (10 g, 60.6 mmol). Keep the internal temperature between 55 – 60 °C by intermittently cooling with an ice bath. Add additional DMSO (10 mL) to keep the slurry stirring. Heat at 70 °C for two hours, then cool to room temperature. Dilute the reaction mixture with water (100 mL) and extract with ether (3 x 50 mL). Wash the organic extracts with 5.0 N HCl (1 X 25 mL) and water (1 X 25 mL). Dry the organic layer over MgSO<sub>4</sub>, filter and concentrate to give the title compound (6.43 g, 96%): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.34 (d, *J* = 6.2 Hz, 2H), 1.56 (m, 1H), 1.46 (m, 4H), 0.93 (t, *J* = 7.3 Hz, 6H).



Part B: 3-Ethylpentylamine

Cool a slurry of LiAlH<sub>4</sub> (4.35 g, 115 mmol) in ether (57 mL) to 0 °C. Allow reaction mixture to gently reflux upon the addition of 3-ethylpentanenitrile (6.38 g, 57.3 mmol). Stir for two hours before quenching with 1.0 N NaOH. Filter the suspension through a Celite<sup>®</sup> pad. Separate the two layers and wash the organic layer with additional 1.0 N NaOH (2 X 25 mL), dry it over Na<sub>2</sub>SO<sub>4</sub>, filter and carefully concentrate to give the title compound: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 2.50 (t, *J* = 7.3 Hz, 2H), 1.24 (m, 7H), 0.080 (t, *J* = 7.0 Hz, 6H).

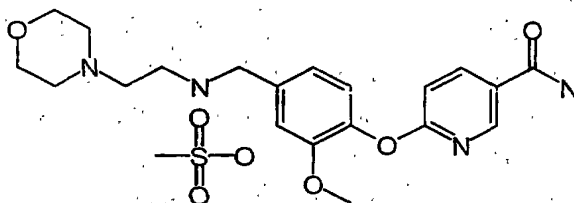


**Part C: 6-{4-[(3-Ethylpentylamino)methyl]-2-methoxyphenoxy}nicotinamide methanesulfonate**

Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), 3-ethylpentylamine (0.111 g, 0.964 mmol) and 3 Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 5% to 15% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and dichloromethane and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.371 g, 84%): TOF MS ES<sup>+</sup> 372.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>30</sub>N<sub>3</sub>O<sub>3</sub> 372.2287 (M+H)<sup>+</sup>, found 372.2271, time 0.32 min; HPLC [Waters XTerra™ C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 23 min], t<sub>R</sub> = 11.9 min, 100% purity.

**Example 734**

**6-{2-Methoxy-4-[(2-morpholin-4-ylethylamino)methyl]phenoxy}nicotinamide**



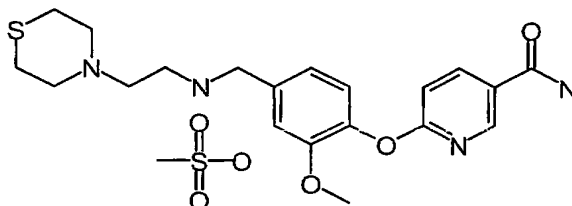
methanesulfonate

Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), 2-morpholin-4-ylethylamine (0.126 g, 0.964 mmol) and 3 Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 5% to 30% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.350 g, 74%): TOF MS ES<sup>+</sup>

387.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>27</sub>N<sub>4</sub>O<sub>4</sub> 387.2032 (M+H)<sup>+</sup>, found 387.2032, time 0.52 min; HPLC [Waters XTerra<sup>TM</sup> C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95 over 23 min], t<sub>R</sub> = 5.7 min, 100% purity.

### Example 735

6-{2-Methoxy-4-[(2-thiomorpholin-4-ylethylamino)methyl]phenoxy}nicotinamide



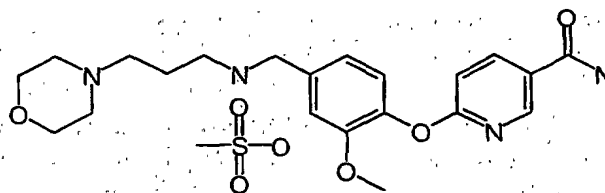
methanesulfonate

Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), 2-thiomorpholin-4-ylethylamine (0.141 g, 0.964 mmol) and 3 Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 5% to 25% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.356 g, 73%): TOF MS ES<sup>+</sup> 403.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>27</sub>N<sub>4</sub>O<sub>3</sub>S 403.1804 (M+H)<sup>+</sup>, found 403.1801, time 0.43 min; HPLC [Waters XTerra<sup>TM</sup> C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 23 min], t<sub>R</sub> = 6.2 min, 100% purity.

### Example 736

6-{2-Methoxy-4-[(3-morpholin-4-ylpropylamino)methyl]phenoxy}nicotinamide  
methanesulfonate

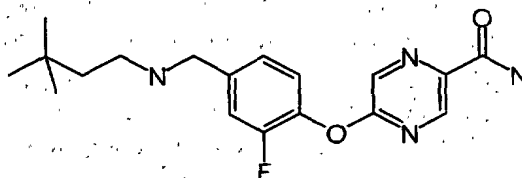
471



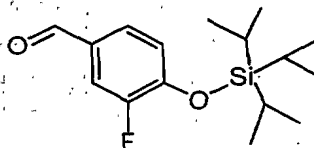
Place 6-(4-formyl-2-methoxyphenoxy)nicotinamide (Example 414, Part B) (0.250 g, 0.918 mmol), 3-morpholin-4-ylpropylamine (0.139 g, 0.964 mmol) and 3 Å molecular sieves in a vial. Add methanol (6.1 mL), cap and stir overnight. Add NaBH<sub>4</sub> (ca. 3-5 eq in two portions) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 5% to 30% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound as a free base. Dissolve the product in methanol and add one equivalent of 0.5 M methanesulfonic acid solution in dichloromethane. Concentrate to give the title compound (0.340 g, 74%): TOF MS ES<sup>+</sup> 401.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>29</sub>N<sub>4</sub>O<sub>4</sub> 401.2189 (M+H)<sup>+</sup>, found 401.2178, time 0.52 min; HPLC [Waters XTerra™ C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 23 min], t<sub>R</sub> = 5.6 min. 100% purity.

### Example 737

5-{4-[(3,3-Dimethylbutylamino)methyl]-2-fluorophenoxy}pyrazine-2-carboxamide



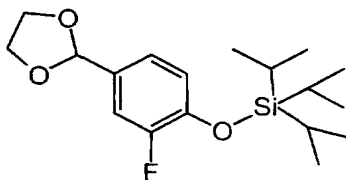
### Part A: 3-Fluoro-4-triisopropylsilanyloxybenzaldehyde



Add triisopropylsilyl chloride (74.32 g, 0.3855 mol), followed by DMF (25 mL), to a solution of 3-fluoro-4-hydroxybenzaldehyde (45.01 g, 0.3213 mol) and imidazole

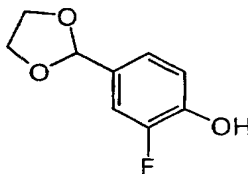
(43.74 g, 0.6425 mole) in DMF (313 mL) at 25-29 °C in a steady stream over 2 min. Stir for 1 hr at room temperature till the reaction complete as determined by HPLC (Column: 4.6 mm x 25 cm Zorbax RX-C8; eluant: 50/50 0.1% TFA:acetonitrile; flow rate 2 mL/min; detector: 230nm; temperature: 22 °C; injection: 10 µL). Pour the reaction mixture into saturated aqueous ammonium chloride solution (1 L) and extract with ether (3 x 1 L). Combine the ether layers, wash with brine (2 x 750 mL) and dried over sodium sulfate. Filter and concentrate to give a yellow oil (106.3g). Purify the crude oil on 1 kg Merck silica gel grade 60 with 20:1 heptane/ethyl acetate (90.14g, 94.6%).

Part B: (4-[1,3]Dioxolan-2-yl-2-fluorophenoxy)triisopropylsilane



Into a 5 L 3-neck flask equipped with a condenser and a Dean-Stark trap add 3-fluoro-4-triisopropylsilanyloxybenzaldehyde (Example 737, Part A) (90.14 g, 0.3041 mol), ethylene glycol (188.75 g, 3.041 mol), and *p*-toluenesulfonic acid (0.58 g, 0.003041 mol) in toluene (3.155 L). Heat to boil and reflux until 130 mL of H<sub>2</sub>O (lower layer) is collected in the Dean-Stark trap (5 hrs). Cool to room temperature, wash with 10% aqueous potassium carbonate solution (2 x 1 L) and brine (2 x 1 L), and dry over sodium sulfate. Filter and concentrate to give the crude product.

Part C: 4-[1,3]Dioxolan-2-yl-2-fluorophenol

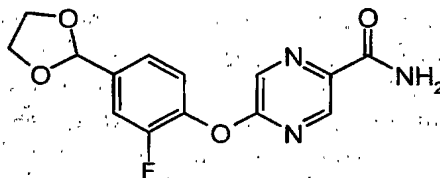


To a solution of (4-[1,3]dioxolan-2-yl-2-fluorophenoxy)triisopropylsilane ( Example 93. Part B) (105.9 g, approximately 0.311 mol) in THF (1.589 L) add 1.0 M tetrabutylammonium fluoride (TBAF) in THF (311 mL) in a steady stream over 5 min at 23-27 °C without cooling. Stir for 1 hr till the reaction complete by TLC (19:1

heptane/ethyl acetate). Concentrate to a red oil and partition between ether (500 mL) and deionized water (1 L). Separate the layers and extract the aqueous layer with ether (500 mL). Combine the ether layers, wash with brine and dry over sodium sulfate. Filter and concentrate to give the crude product (92.9 g). Dissolve the crude product in dichloromethane and filter through 400 g of silica gel 60. Wash with dichloromethane (3 x 1 L fractions) and concentrate the combined filtrate to give an impure product.

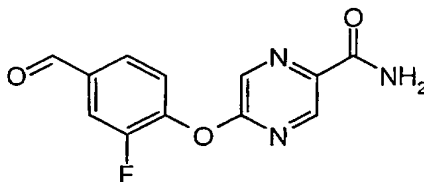
Crystallize from dichloromethane/heptane to give the title compound (29.8 g, 52%). Gas chromatography: retention time 15.96 min (30 m x 0.32 mm i.d. DB-1 column, 0.25 micron film thickness; 1.2 mL/min flow rate; 55:1 split ratio; temperature profile: 35 °C/3 min, 10 °C temperature increase per min; 250 °C/10.5 min). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 3.84-3.93 (m, 2H, CH<sub>2</sub>), 3.93-4.04 (m, 2H, CH<sub>2</sub>), 5.60 (s, 1H, CH), 6.91 (t, 1H, ArH), 7.06 (dd, 1H, ArH), 7.15 (dd, 1H, ArH), 10.0 (s, 1H, OH).

Part D: 5-(4-[1,3]Dioxolan-2-yl-2-fluorophenoxy)pyrazine-2-carboxamide



Heat a mixture of 5-chloropyrazine-2-carboxamide (14.18 g, 0.09 mol) (*see* S. Fujii, T. Takagi, S. Toshihisa, M. Seki, Agric. Biol. Chem., 1982, 46, (8), 2169), 4-[1,3]dioxolan-2-yl-2-fluorophenol (Example 737, Part C) (16.58 g, 0.09 mole), and powdered potassium carbonate (31.10 g, 0.225 mol) in DMF (213 mL) at 100 °C for 2 hours. Dilute the reaction mixture to 1 L with deionized water, filter at room temperature, and wash the filter cake with water. Extract the filtrate with ether (2 x 1 L) and dry the extracts over sodium sulfate. Combine the filter cake and ether extracts and concentrate to dryness to give a semi-solid (32.81 g) containing residual water and DMF (by <sup>1</sup>H NMR). Recrystallize a portion from ethyl acetate to give a purified sample: mp 169-172 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 3.94-4.03 (m, 2H, CH<sub>2</sub>), 4.03-4.11 (m, 2H, CH<sub>2</sub>), 5.78 (s, 1H, CH), 7.36 (d, 1H, ArH), 7.46 (t, 2H, ArH), 7.73 (s, 1H, HetH), 8.13 (s, 1H, HetH), 8.68 (d, 2H, amide); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 64.879, 101.364, 114.869, 123.251, 123.762, 132.997, 137.855, 139.454, 140.340, 140.744, 152.019, 154.475, 159.643, 164.135; MS (ES<sup>+</sup>): m/z 306.0 (M+H).

## Part E: 5-(2-Fluoro-4-formylphenoxy)pyrazine-2-carboxamide



Combine formic acid (90%, 453 mL) and crude 5-(4-[1,3]dioxolan-2-yl)-2-fluorophenoxy)pyrazine-2-carboxamide (Example 737, Part D) (32.81 g, approximately 0.09 mole) and stir initially a clear yellow solution, which becomes a thick slurry in an hour at room temperature. Stir overnight at room temperature till the reaction complete by HPLC. Quench the reaction with deionized water (1 L) and extract with dichloromethane (4 x 4 L). Combine the extracts and mix with aqueous sodium bicarbonate solution. Concentrate on a rotary evaporator to give a slurry of a solid in water (when the separation of layers not possible). Extract the mixture with ethyl acetate (4 x 1 L) and concentrate the combined extracts to a yellow solid (29.65 g). Form slurries successively four times with boiling methanol (1 L) and filter while hot. Combine the filter cakes and dissolve in enough boiling methanol to give a clear solution. Concentrate the solution to approximately 1 liter and allow to crystallize at 0 °C. Filter the resulting slurry at 0 °C and dry the filter cake under vacuum at room temperature to give the title compound (17.79 g, 75.7%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.70 (t, 1H, ArH), 7.78 (s, 1H, HetH), 7.86-7.93 (m, 2H, ArH), 8.14 (s, 1H, HetH), 8.73 (d, 2H, amide), 10.0 (s, 1H, CHO); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 116.884, 124.606, 126.980, 133.186, 134.967, 140.765, 144.016, 152.493, 154.974, 159.276, 164.057, 190.777; MS (ES+) *m/z* 262.3 (M+H).

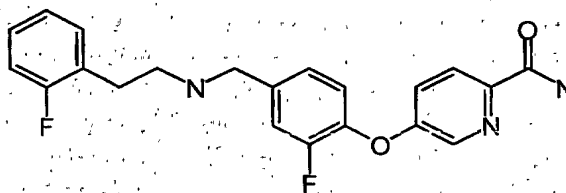
## Part F: 5-{4-[(3,3-Dimethylbutylamino)methyl]-2-fluorophenoxy}pyrazine-2-carboxamide

Place 5-(2-fluoro-4-formylphenoxy)pyrazine-2-carboxamide (Example 737, Part E) (0.350 g, 1.14 mmol), 3,3-dimethylbutylamine (0.19 g, 1.41 mmol) and 3 Å molecular sieves in a vial. Add methanol (9.7 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.053 g, 1.41 mmol) and stir until the gasses stop evolving. Filter the reaction mixture, then concentrate. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 6% to 30% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound (0.225 g, 49%): TOF MS

ES<sup>+</sup> 347.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>F 347.1883 (M+H)<sup>+</sup>, found 347.1883, time 0.53 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 10.9 min, 100% purity.

### Example 738

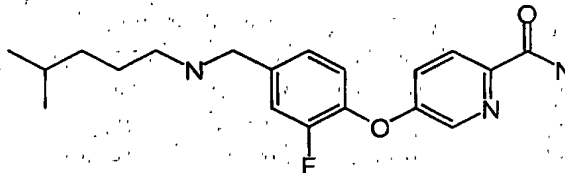
5-(2-Fluoro-4-{{[2-(2-fluorophenyl)ethylamino]methyl}phenoxy}pyridine-2-carboxamide



Place 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.650 g, 2.50 mmol), 2-fluorophenethylamine (0.382 g, 2.75 mmol) and 3 Å molecular sieves in a vial. Add methanol (12 mL), cap and stir overnight. Add NaBH<sub>4</sub> (slight excess) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 0% to 10% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound (0.718 g, 75%): TOF MS ES<sup>+</sup> 384.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>20</sub>N<sub>3</sub>O<sub>2</sub>F<sub>2</sub> 387.2032 (M+H)<sup>+</sup>, found 387.2032, time 0.52 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 11.4 min, 100% purity.

### Example 739

5-{2-Fluoro-4-[(4-methylpentylamino)methyl]phenoxy}pyridine-2-carboxamide

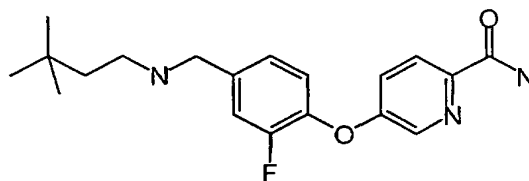


Place 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.650 g, 2.50 mmol), 4-methylpentylamine (Example 433, Part A) (0.278 g, 2.75

mmol) and 3 Å molecular sieves in a vial. Add methanol (12 mL), cap and stir overnight. Add NaBH<sub>4</sub> (slight excess) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 0% to 10% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound (0.470 g, 55%): TOF MS ES<sup>+</sup> 346.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>F 346.1931 (M+H)<sup>+</sup>, found 346.1922, time 0.48 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 11.6 min, 100% purity.

#### Example 740

5-{4-[(3,3-Dimethylbutylamino)methyl]-2-fluorophenoxy}pyridine-2-carboxamide



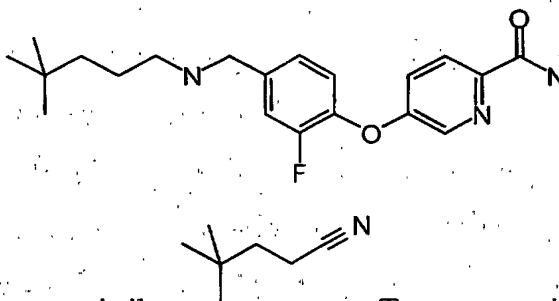
Place 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.650 g, 2.50 mmol), 3,3-dimethylbutylamine (0.278 g, 2.75 mmol) and 3 Å molecular sieves in a vial. Add methanol (12 mL), cap and stir overnight. Add NaBH<sub>4</sub> (slight excess) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 0% to 10% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound (0.543 g, 63%): TOF MS ES<sup>+</sup> 346.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>F 346.1931 (M+H)<sup>+</sup>, found 346.1921, time 0.48 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 11.3 min, 100% purity.

#### Example 741

5-{4-[(4,4-Dimethylpentylamino)methyl]-2-fluorophenoxy}pyridine-2-carboxamide

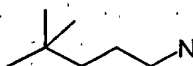


477

**Part A: 4,4-Dimethylpentanenitrile**

To a suspension of sodium cyanide

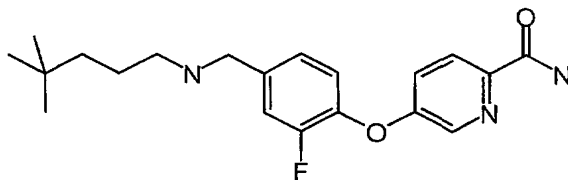
(3.33 g, 67.8 mmol) in DMSO (34 mL) at 60 °C, slowly add 1-bromo-3,3-dimethylbutane (10 g, 60.6 mmol). Keep the internal temperature between 55 – 65 °C by intermittently cooling with an ice bath. Heat at 70 °C for 1.5 hours, then cool to room temperature. Dilute the reaction mixture with water (100 mL) and extract with ether (3 x 50 mL). Wash the organic extracts with 5.0 N HCl (1 X 25 mL) and water (1 X 25 mL). Dry the organic layer over MgSO<sub>4</sub>, filter and concentrate to give the title compound (6.66 g, 98%): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.29 (t, *J* = 8.1 Hz, 2H), 1.63 (t, *J* = 8.1 Hz, 2H), 0.94 (s, 9H).

**Part B: 4,4-Dimethylpentylamine**

Cool a slurry of LiAlH<sub>4</sub> (4.30 g, 113 mmol) in ether (57 mL) to -30 °C. Allow reaction mixture to gently reflux upon the addition of 4,4-dimethylpentanenitrile (6.29 g, 56.6 mmol). Heat at reflux for an additional 45 minutes. Cool the reaction mixture to room temperature before quenching with 1.0 N NaOH. Filter the suspension through a Celite<sup>®</sup> pad. Separate the two layers and wash the organic layer with additional 1.0 N NaOH (2 X 25 mL), dry it over Na<sub>2</sub>SO<sub>4</sub>, filter and carefully concentrate to give the title compound: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.68 (m, 2H), 2.17 (bs, 2H), 1.44 (m, 2H), 1.18 (t, *J* = 11.0 Hz, 2H), 0.88 (s, 9H).

**Part C: 5-{4-[(4,4-Dimethylpentylamino)methyl]-2-fluorophenoxy}pyridine-2-carboxamide**

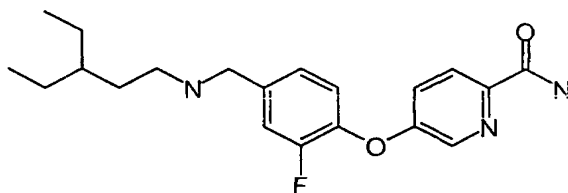
478



Place 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.650 g, 2.50 mmol), 4,4-dimethylpentylamine (0.317 g, 2.75 mmol) and 3 Å molecular sieves in a vial. Add methanol (12 mL), cap and stir overnight. Add NaBH<sub>4</sub> (slight excess) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 0% to 10% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound (0.248 g, 28%): TOF MS ES<sup>+</sup> 360.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>F 360.2087 (M+H)<sup>+</sup>, found 360.2076, time 0.48 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 12.3 min, 98.2% purity.

#### Example 742

5-{4-[(3-Ethylpentylamino)methyl]-2-fluorophenoxy}pyridine-2-carboxamide

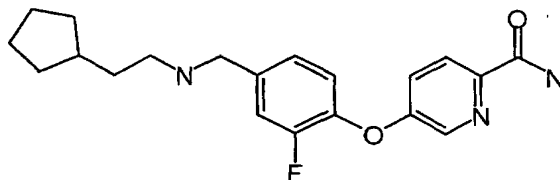


Place 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.650 g, 2.50 mmol), 3-ethylpentylamine (Example 733, Part B) (0.317 g, 2.75 mmol) and 3 Å molecular sieves in a vial. Add methanol (12 mL), cap and stir overnight. Add NaBH<sub>4</sub> (slight excess) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 0% to 10% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound (0.516 g, 58%): TOF MS ES<sup>+</sup> 360.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>F 360.2087 (M+H)<sup>+</sup>, found 360.2086, time 0.53 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm),

0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18],  $t_R$  = 12.3 min, 100% purity.

#### Example 743

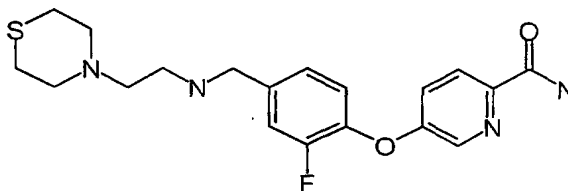
5-{4-[(2-Cyclopentylethylamino)methyl]-2-fluorophenoxy}pyridine-2-carboxamide



Place 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.650 g, 2.50 mmol), 2-cyclopentylethylamine (0.792 g, 2.75 mmol) and 3 Å molecular sieves in a vial. Add methanol (12 mL), cap and stir overnight. Add  $\text{NaBH}_4$  (slight excess) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 0% to 10% (2.0 M  $\text{NH}_3$  in methanol) in ethyl acetate to give the title compound (0.0850 g, 10%): TOF MS  $\text{ES}^+$  358.2 ( $\text{M}+\text{H}$ )<sup>+</sup>, HRMS calcd for  $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_2\text{F}$  358.1931 ( $\text{M}+\text{H}$ )<sup>+</sup>, found 358.1925, time 0.48 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18],  $t_R$  = 11.8 min, 94.2% purity.

#### Example 744

5-{2-Fluoro-4-[(2-thiomorpholin-4-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide

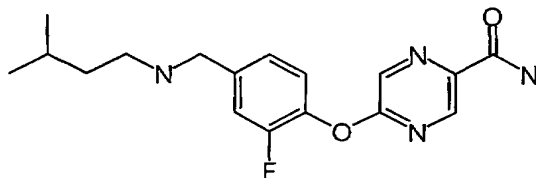


Place 5-(2-fluoro-4-formylphenoxy)pyridine-2-carboxamide (Example 403, Part B) (0.650 g, 2.50 mmol), 2-thiomorpholin-4-ylethylamine (0.402 g, 2.75 mmol) and 3 Å molecular sieves in a vial. Add methanol (12 mL), cap and stir overnight. Add  $\text{NaBH}_4$

(slight excess) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 0% to 30% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate to give the title compound (0.792 g, 81%): TOF MS ES<sup>+</sup> 391.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>FS 391.1604 (M+H)<sup>+</sup>, found 391.1594, time 0.48 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 6.7 min, 100% purity.

### Example 745

5-{2-Fluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-pyrazine-2-carboxylic acid



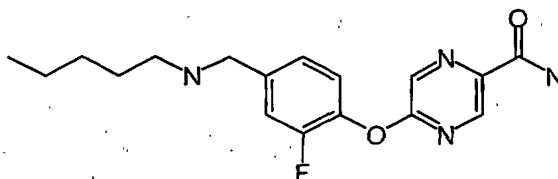
amide

Place 5-(2-fluoro-4-formylphenoxy)pyrazine-2-carboxamide (Example 737, Part E) (0.400 g, 1.53 mmol), isoamylamine (0.147g, 1.68 mmol) and 3 Å molecular sieves in a vial. Add methanol (7.7 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.058 g, 1.53 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 0% to 15% (2.0 M NH<sub>3</sub> in methanol) in 80% (ethyl acetate in hexanes) to give the title compound (0.225 g, 50%): TOF MS ES<sup>+</sup> 333.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>17</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>F 333.1727 (M+H)<sup>+</sup>, found 333.1714, time 0.55 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 10.1 min, 100% purity.

### Example 746

5-(2-Fluoro-4-pentylaminomethylphenoxy)pyrazine-2-carboxamide

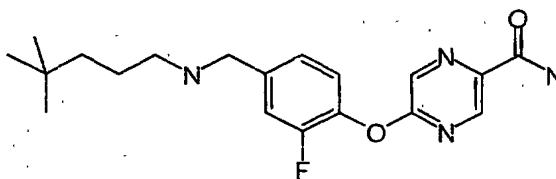
481



Place 5-(2-fluoro-4-formylphenoxy)pyrazine-2-carboxamide (Example 737, Part E) (0.400 g, 1.53 mmol), amylamine (0.147g, 1.68 mmol) and 3Å molecular sieves in a vial. Add methanol (7.7 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.058 g, 1.53 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column 0% to 15% (2.0 M NH<sub>3</sub> in methanol) in 80% (ethyl acetate in hexanes) to give the title compound (0.334 g, 66%): TOF MS ES<sup>+</sup> 333.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>17</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>F 333.1727 (M+H)<sup>+</sup>, found 333.1722, time 0.53 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 10.3 min, 96.8% purity.

#### Example 747

5-{4-[(4,4-Dimethylpentylamino)methyl]-2-fluorophenoxy}pyrazine-2-carboxamide

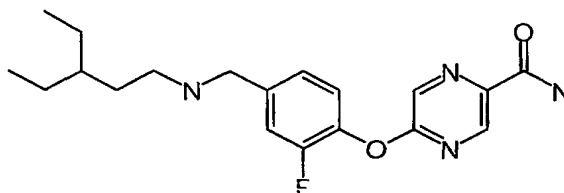


Place 5-(2-fluoro-4-formylphenoxy)pyrazine-2-carboxamide (Example 737, Part E) (0.400 g, 1.53 mmol), 4,4-dimethylpentylamine (0.194g, 1.68 mmol) (Example 97, Part B) and 3Å molecular sieves in a vial. Add methanol (7.7 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.058 g, 1.53 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 0% to 15% (2.0 M NH<sub>3</sub> in methanol) in 80% (ethyl acetate in hexanes). Concentrate the fractions containing the product. Take the solid up in dichloromethane (100 mL) and wash with 1.0 N NaOH (2 X 25 mL) to give the title compound (0.314 g, 57%): TOF MS ES<sup>+</sup> 361.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub>F 361.2040 (M+H)<sup>+</sup>, found 361.2042,

time 0.55 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18],  $t_R$  = 12.0 min, 100% purity.

### Example 748

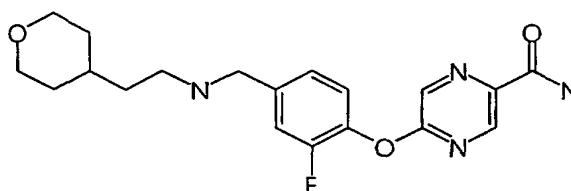
5-{4-[(3-Ethylpentylamino)methyl]-2-fluorophenoxy}pyrazine-2-carboxamide



Place 5-(2-fluoro-4-formylphenoxy)pyrazine-2-carboxamide (Example 737, Part E) (0.400 g, 1.53 mmol), 3-ethylpentylamine (0.194g, 1.68 mmol) (Example 733, Part B) and 3 Å molecular sieves in a vial. Add methanol (7.7 mL), cap and stir overnight. Add  $\text{NaBH}_4$  (0.058 g, 1.53 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 0% to 15% (2.0 M  $\text{NH}_3$  in methanol) in 80% (ethyl acetate in hexanes) to give the title compound (0.342 g, 62%): TOF MS  $\text{ES}^+$  361.2 ( $\text{M}+\text{H}^+$ ), HRMS calcd for  $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_2\text{F}$  361.2040 ( $\text{M}+\text{H}^+$ ), found 361.2048, time 0.57 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18],  $t_R$  = 12.0 min, 96.9% purity.

### Example 749

5-(2-Fluoro-4-{[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)pyrazine-2-carboxamide

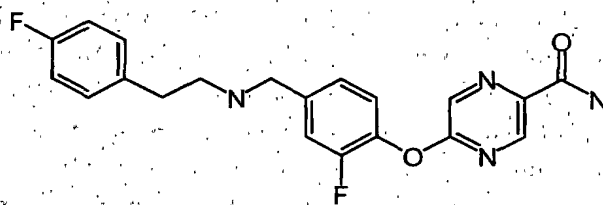


Place 5-(2-fluoro-4-formylphenoxy)pyrazine-2-carboxamide (Example 737, Part E) (0.400 g, 1.53 mmol), 2-(tetrahydropyran-4-yl)ethylamine (0.217g, 1.68 mmol) and

3 Å molecular sieves in a vial. Add methanol (7.7 mL), cap and stir overnight. Add  $\text{NaBH}_4$  (0.058 g, 1.53 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 0% to 30% (2.0 M  $\text{NH}_3$  in methanol) in 80% (ethyl acetate in hexanes) to give the title compound (0.385 g, 67%): TOF MS  $\text{ES}^+$  375.2 ( $\text{M}+\text{H}$ ) $^+$ , HRMS calcd for  $\text{C}_{19}\text{H}_{24}\text{N}_4\text{O}_3\text{F}$  375.1832 ( $\text{M}+\text{H}$ ) $^+$ , found 375.1847, time 0.53 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18],  $t_R$  = 8.6 min, 95.4% purity.

#### Example 750

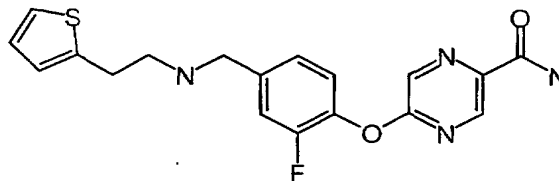
5-(2-Fluoro-4-{{[2-(4-fluorophenyl)ethylamino]methyl}phenoxy}pyrazine-2-carboxamide



Place 5-(2-fluoro-4-formylphenoxy)pyrazine-2-carboxamide (Example 737, Part E) (0.400 g, 1.53 mmol), 4-fluorophenethylamine (0.234g, 1.68 mmol) and 3 Å molecular sieves in a vial. Add methanol (7.7 mL), cap and stir overnight. Add  $\text{NaBH}_4$  (0.058 g, 1.53 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 0% to 15% (2.0 M  $\text{NH}_3$  in methanol) in 80% (ethyl acetate in hexanes). Concentrate the fractions containing the product. Take the solid up in dichloromethane (100 mL) and wash with 1.0 N NaOH (2 X 25 mL) to give the title compound (0.383 g, 65%): TOF MS  $\text{ES}^+$  385.1 ( $\text{M}+\text{H}$ ) $^+$ , HRMS calcd for  $\text{C}_{20}\text{H}_{19}\text{N}_4\text{O}_2\text{F}_2$  385.1476 ( $\text{M}+\text{H}$ ) $^+$ , found 385.1480, time 0.55 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18],  $t_R$  = 11.1 min, 100% purity.

**Example 751**

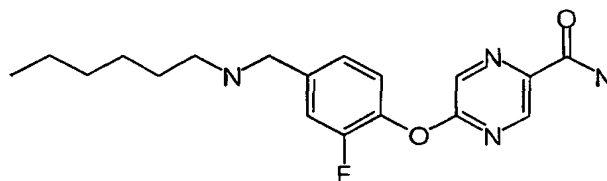
5-{2-Fluoro-4-[(2-thiophen-2-ylethylamino)methyl]phenoxy}pyrazine-2-carboxamide



Place 5-(2-fluoro-4-formylphenoxy)pyrazine-2-carboxamide (Example 737, Part E) (0.400 g, 1.53 mmol), 2-(2-thienyl)ethylamine (0.217g, 1.68 mmol) and 3Å molecular sieves in a vial. Add methanol (7.7 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.058 g, 1.53 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 0% to 15% (2.0 M NH<sub>3</sub> in methanol) in 80% (ethyl acetate in hexanes). Concentrate the fractions containing the product. Take the solid up in dichloromethane (100 mL) and wash with 1.0 N NaOH (2 X 25 mL) to give the title compound (0.100 g, 18%): TOF MS ES<sup>+</sup> 373.1 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>FS 373.1135 (M+H)<sup>+</sup>, found 373.1150, time 0.48 min: HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 10.3 min. 100% purity.

**Example 752**

5-(2-Fluoro-4-hexylaminomethylphenoxy)pyrazine-2-carboxamide



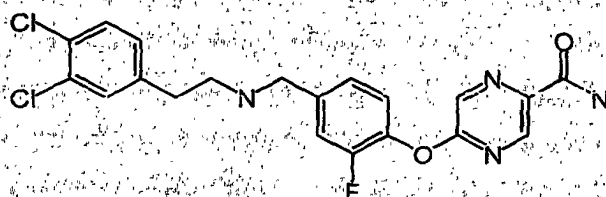
Place 5-(2-fluoro-4-formylphenoxy)pyrazine-2-carboxamide (Example 737, Part E) (0.400 g, 1.53 mmol), hexylamine (0.170g, 1.68 mmol) and 3Å molecular sieves in a vial. Add methanol (7.7 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.058 g, 1.53 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 0% to 15% (2.0 M NH<sub>3</sub> in methanol) in



80% (ethyl acetate in hexanes) to give the title compound (0.329 g, 62%): TOF MS ES<sup>+</sup> 347.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>F 347.1883 (M+H)<sup>+</sup>, found 347.1897, time 0.57 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 11.4 min, 94.8% purity.

### Example 753

5-(4-{[2-(3,4-Dichlorophenyl)ethylamino]methyl}-2-fluorophenoxy)pyrazine-2-



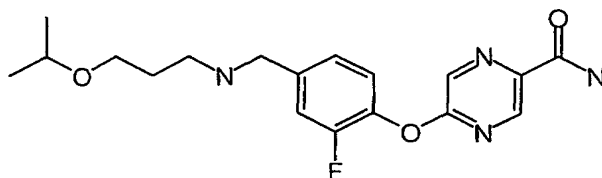
carboxamide

Place 5-(2-fluoro-4-formylphenoxy)pyrazine-2-carboxamide (Example 737, Part E) (0.400 g, 1.53 mmol), 3,4-dichlorophenethylamine (0.320 g, 1.68 mmol) and 3Å molecular sieves in a vial. Add methanol (7.7 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.058 g, 1.53 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 0% to 15% (2.0 M NH<sub>3</sub> in methanol) in 80% (ethyl acetate in hexanes). Concentrate the fractions containing the product. Take the solid up in dichloromethane (100 mL) and wash with 1.0 N NaOH (2 X 25 mL) to give the title compound (0.293 g, 44%): TOF MS ES<sup>+</sup> 435.1 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>FCl<sub>2</sub> 435.0791 (M+H)<sup>+</sup>, found 435.0815, time 0.53 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 12.8 min, 100% purity.

### Example 754

5-{2-Fluoro-4-[(3-isopropoxypropylamino)methyl]phenoxy}pyrazine-2-carboxamide

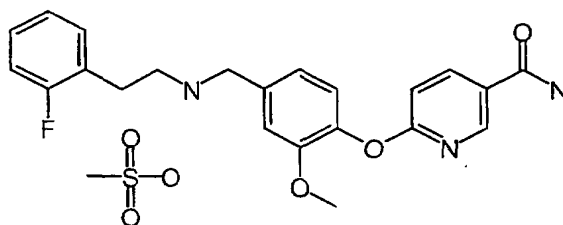
486



Place 5-(2-fluoro-4-formylphenoxy)pyrazine-2-carboxamide (Example 737, Part E) (0.400 g, 1.53 mmol), 3-isopropoxypropylamine (0.197g, 1.68 mmol) and 3 Å molecular sieves in a vial. Add methanol (7.7 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.058 g, 1.53 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 0% to 30% (2.0 M NH<sub>3</sub> in methanol) in 80% (ethyl acetate in hexanes). Concentrate the fractions containing the product. Take the solid up in dichloromethane (100 mL) and wash with 1.0 N NaOH (2 X 25 mL) to give the title compound (0.395 g, 71%): TOF MS ES<sup>+</sup> 363.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>F 363.1832 (M+H)<sup>+</sup>, found 363.1821, time 0.57 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 9.8 min, 100% purity.

### Example 755

6-(4-{{2-(2-Fluorophenyl)ethylamino}methyl}-2-methoxyphenoxy)nicotinamide



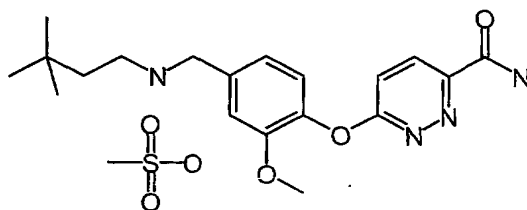
methanesulfonate

Dissolve 6-(4-{{2-(2-fluorophenyl)ethylamino}methyl}-2-methoxyphenoxy)nicotinamide (Example 431) (0.701, 1.18 mmol) in methanol (4.4 mL) and dichloromethane (4.4 mL). Add 0.5 M methanesulfonic acid (3.54 mL, 1.18 mmol) in dichloromethane. Stir for 10 minutes, then concentrate to give the title compound (0.875 g, ~100%): TOF MS ES<sup>+</sup> 396.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>F 396.1723 (M+H)<sup>+</sup>, found 396.1739, time 0.53 min; HPLC [Waters XTerra<sup>TM</sup> MS C-18 (150 x 4.6

mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95% over 15 min],  $t_R$  = 10.8 min, 100% purity.

### Example 756

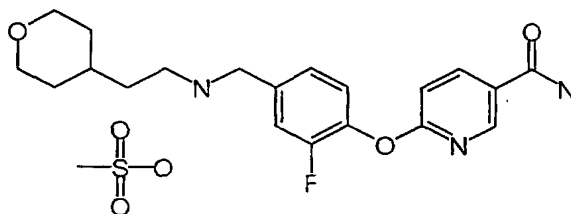
6-{4-[(3,3-Dimethylbutylamino)methyl]-2-methoxyphenoxy}pyridazine-3-carboxamide methanesulfonate



Place 6-(4-formyl-2-methoxyphenoxy)pyridazine-3-carboxamide (Example 721, Part C) (0.406 g, 1.49 mmol), 3,3-dimethylbutylamine (0.216 mL, 1.56 mmol) and 3 Å molecular sieves in a vial. Add methanol (7.4 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.060 g, 1.56 mmol) and stir until the gasses stop evolving. Filter the reaction mixture, then concentrate it. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 6% to 30% (2.0 M NH<sub>3</sub> in methanol) in 80% (ethyl acetate in hexanes) to give the title compound as a free base (0.378 g, 71%). Dissolve the free base (0.357, 0.99 mmol) in methanol (2.5 mL) and dichloromethane (2.5 mL). Add 0.5 M methanesulfonic acid (1.99 mL, 0.99 mmol) in dichloromethane. Stir for 10 minutes, then concentrate to give the title methanesulfonic acid salt (0.476 g, ~100%): TOF MS ES<sup>+</sup> 359.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>27</sub>N<sub>4</sub>O<sub>3</sub> 359.2083 (M+H)<sup>+</sup>, found 359.2099, time 0.53 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18],  $t_R$  = 10.7 min, 96.8% purity.

### Example 757

6-(2-Fluoro-4-{[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)nicotinamide

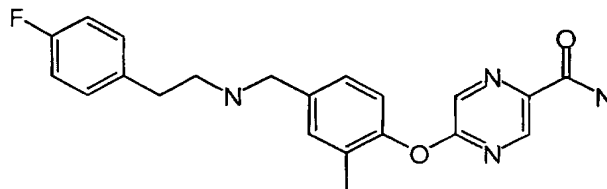


methanesulfonate

Place 6-(2-fluoro-4-formylphenoxy)nicotinamide (Example 223, step 1) (0.700 g, 2.69 mmol), 2-(tetrahydropyran-4-yl)ethylamine (0.348 g, 2.69 mmol) and 3 Å molecular sieves in a vial. Add methanol (13.5 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.204 g, 5.38 mmol) and stir until the gasses stop evolving. Filter the reaction mixture, then concentrate it. Purify by chromatography eluting with 0% to 20% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate over 1 hour at 20 mL / min to give 6-(2-fluoro-4-{{2-(tetrahydropyran-4-yl)ethylamino}methyl}phenoxy)nicotinamide (0.717 g, 71.3%). Dissolve the compound in dichloromethane: methanol (10 mL) and add 1 equivalent of 0.50 M methanesulfonic acid in dichloromethane. Stir the solution for a short time before concentrating to give the title compound (0.904 g): TOF MS ES<sup>+</sup> 374.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>F 374.1880 (M+H)<sup>+</sup>, found 374.1881, time 0.55 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 8.7 min, 100% purity.

#### Example 758

5-(4-{{2-(4-Fluorophenyl)ethylamino}methyl}-2-methylphenoxy)pyrazine-2-carboxamide

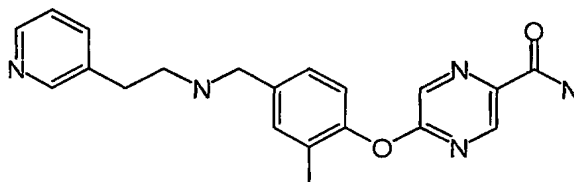


Place 5-(4-formyl-2-methylphenoxy)pyrazine-2-carboxamide (Example 404, part D) (0.600 g, 2.33 mmol), 2-(4-fluorophenyl)ethylamine (0.325 g, 2.33 mmol) and 3 Å molecular sieves in a vial. Add methanol (11.7 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.088 g, 2.33 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 5% to 20% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate. Concentrate the fraction containing the product, then take it up in EtOAc (100mL). Wash the organic solution with 1.0 N NaOH (2 X 25 mL), dry it over Na<sub>2</sub>SO<sub>4</sub> and concentrate it to give the title compound (0.478 g, 54.0%): TOF MS ES<sup>+</sup> 381.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>F 381.1727 (M+H)<sup>+</sup>, found 381.1729, time 0.39 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm),

0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18],  $t_R$  = 11.3 min, 97.8% purity.

### Example 759

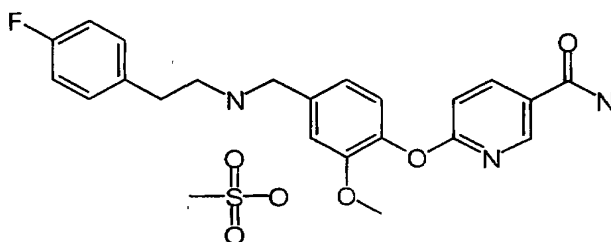
5-{2-Methyl-4-[(2-pyridin-3-yl-ethylamino)methyl]phenoxy}pyrazine-2-carboxamide



Place 5-(4-formyl-2-methylphenoxy)pyrazine-2-carboxamide (Example 404, part D) (0.600 g, 2.33 mmol), 2-pyridin-3-ylethylamine (0.285 g, 2.33 mmol) and 3 Å molecular sieves in a vial. Add methanol (11.7 mL), cap and stir overnight. Add  $\text{NaBH}_4$  (0.088 g, 2.33 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 5% to 25% (2.0 M  $\text{NH}_3$  in methanol) in ethyl acetate. Concentrate the fraction containing the product, then take it up in EtOAc (100mL). Wash the organic solution with 1.0 N NaOH (2 X 25 mL), dry it over  $\text{Na}_2\text{SO}_4$  and concentrate it to give the title compound (0.315 g, 37.2%): TOF MS  $\text{ES}^+$  364.2 ( $\text{M}+\text{H}$ )<sup>+</sup>, HRMS calcd for  $\text{C}_{20}\text{H}_{22}\text{N}_5\text{O}_2$  364.1773 ( $\text{M}+\text{H}$ )<sup>+</sup>, found 367.1774, time 0.39 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18],  $t_R$  = 6.1 min, 100% purity.

### Example 760

6-(4-{[2-(4-Fluorophenyl)ethylamino]methyl}-2-methoxyphenoxy)nicotinamide

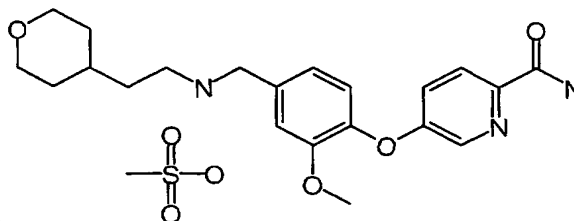


methanesulfonate

Dissolve 6-(4-{[2-(4-fluorophenyl)ethylamino]methyl}-2-methoxyphenoxy)nicotinamide (Example 430) (8.40 g, 2.12 mmol) in dichloromethane:methanol (1:1) (4.25 mL) and add 1 equivalent of 0.50 M methanesulfonic acid in dichloromethane. Stir the solution for a short time before concentrating to give the title compound (0.102 g): TOF MS ES<sup>+</sup> 396.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>, F 396.1723 (M+H)<sup>+</sup>, found 396.1731, time 0.39 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 10.9 min, 100% purity.

### Example 761

5-(2-Methoxy-4-{[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)pyridine-2-

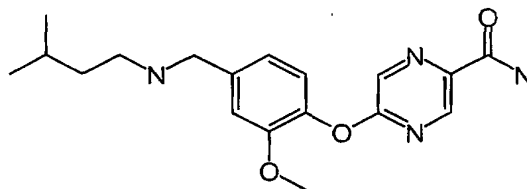


carboxamide methanesulfonate

Place 5-(4-formyl-2-methoxyphenoxy)pyridine-2-carboxamide (Ex 391, Part A) (0.600 g, 2.20 mmol), 2-(tetrahydropyran-4-yl)ethylamine (0.285 g, 2.20 mmol) and 3 Å molecular sieves in a vial. Add methanol (11.0 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.0833 g, 2.20 mmol) and stir until the gasses stop evolving. Filter the reaction mixture, then concentrate it. Purify by chromatography eluting with 5% to 30% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate over 45 minutes to give 5-(2-methoxy-4-{[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide (0.6103 g, 71.9%). Dissolve the compound in dichloromethane:methanol (3.2 mL) and add 1 equivalent of 0.50 M methanesulfonic acid in dichloromethane. Stir the solution for a short time before concentrating to give the title compound (0.775 g): TOF MS ES<sup>+</sup> 386.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>4</sub> 386.2080 (M+H)<sup>+</sup>, found 386.2078, time 0.39 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 9.3 min, 100% purity.

**Example 762**

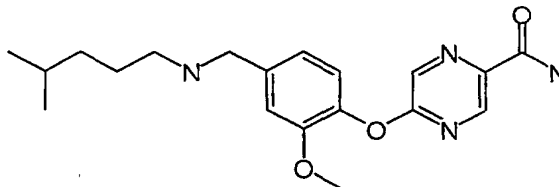
5-{2-Methoxy-4-[(3-methylbutylamino)methyl]phenoxy}pyrazine-2-carboxamide



Place 5-(4-formyl-2-methoxyphenoxy)pyrazine-2-carboxamide (Example 719, Part A) (0.700 g, 2.56 mmol), isoamylamine (0.234 g, 2.69 mmol) and 3 Å molecular sieves in a vial. Add methanol (12.8 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.0969 g, 2.56 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 5% to 20% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate over 45 minutes. Concentrate the fraction containing the product, and dissolve it in EtOAc (100mL). Wash the organic solution with 1.0 N NaOH (2 X 25 mL), dry it over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate to give the title compound (0.484 g, 54.9%): TOF MS ES<sup>+</sup> 345.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>25</sub>N<sub>4</sub>O<sub>3</sub> 345.1927 (M+H)<sup>+</sup>, found 345.1938, time 0.38 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 10.1 min, 95.4% purity.

**Example 763**

5-{2-Methoxy-4-[(4-methylpentylamino)methyl]phenoxy}pyrazine-2-carboxamide

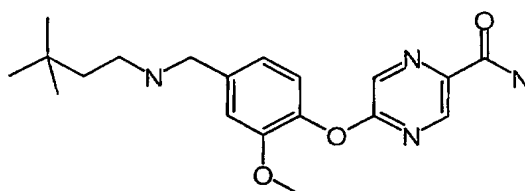


Place 5-(4-formyl-2-methoxyphenoxy)pyrazine-2-carboxamide (Example 719, Part A) (0.700 g, 2.56 mmol), 4-methylpentylamine (Example 433, Part A) (0.272 g, 2.69 mmol) and 3 Å molecular sieves in a vial. Add methanol (12.8 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.0969 g, 2.56 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column

in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 5% to 20% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate over 45 minutes. Concentrate the fraction containing the product, then take it up in EtOAc (100mL). Wash the organic solution with 1.0 N NaOH (2 X 25 mL), dry it over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. Dissolve the product in ether:dichloromethane (5:1) (25 mL), add hexanes (20 mL), and then concentrate to about a quarter of the volume. Filter the precipitate to give the title compound (0.335 g, 36.5%): TOF MS ES<sup>+</sup> 359.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>27</sub>N<sub>4</sub>O<sub>3</sub> 359.2083 (M+H)<sup>+</sup>, found 359.2087, time 0.38 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 11.3 min, 100% purity.

#### Example 764

5-{4-[(3,3-Dimethylbutylamino)methyl]-2-methoxyphenoxy}pyrazine-2-carboxamide

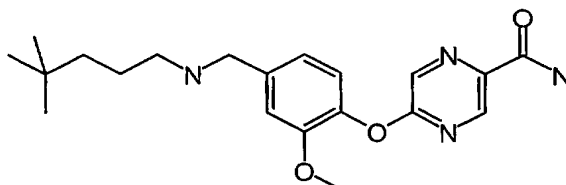


Place 5-(4-formyl-2-methoxyphenoxy)pyrazine-2-carboxamide (Example 719, Part A) (0.700 g, 2.56 mmol), 3,3-dimethylbutylamine (0.272 g, 2.69 mmol) and 3 Å molecular sieves in a vial. Add methanol (12.8 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.0969 g, 2.56 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 5% to 20% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate over 45 minutes. Concentrate the fraction containing the product, then take it up in EtOAc (100mL). Wash the organic solution with 1.0 N NaOH (2 X 25 mL), dry it over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. Dissolve the product in ether:dichloromethane (5:1) (25 mL), add hexanes (20 mL), and then concentrate to about a quarter of the volume. Filter the precipitate to give the title compound (0.421 g, 45.9%): TOF MS ES<sup>+</sup> 359.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>19</sub>H<sub>27</sub>N<sub>4</sub>O<sub>3</sub> 359.2083 (M+H)<sup>+</sup>, found 359.2093, time 0.38 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 11.0 min, 98.0% purity.



**Example 765**

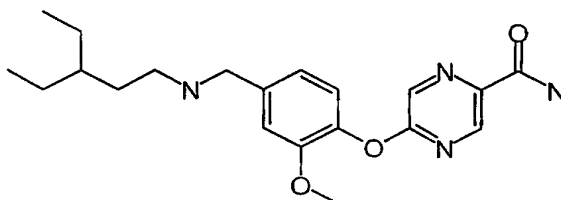
5-{4-[(4,4-Dimethylpentylamino)methyl]-2-methoxyphenoxy}pyrazine-2-carboxamide



Place 5-(4-formyl-2-methoxyphenoxy)pyrazine-2-carboxamide (Example 719, Part A) (0.700 g, 2.56 mmol), 4,4-dimethylpentylamine (0.310 g, 2.69 mmol) and 3 Å molecular sieves in a vial. Add methanol (12.8 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.0969 g, 2.56 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO® pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO® column with 5% to 20% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate over 45 minutes. Concentrate the fraction containing the product, then add EtOAc (100mL). Wash the organic solution with 1.0 N NaOH (2 X 25 mL), dry it over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. Dissolve the product in ether:dichloromethane (5:1) (25 mL), add hexanes (20 mL), and then concentrate to about a quarter of the volume. Filter the precipitate to give the title compound (0.356 g, 37.3%): TOF MS ES<sup>+</sup> 373.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>29</sub>N<sub>4</sub>O<sub>3</sub> 373.2240 (M+H)<sup>+</sup>, found 373.2245, time 0.39 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 12.0 min, 98.7% purity.

**Example 766**

5-{4-[(3-Ethylpentylamino)methyl]-2-methoxyphenoxy}pyrazine-2-carboxamide

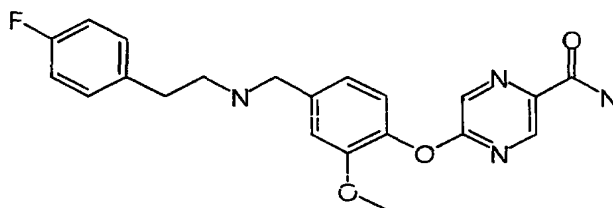


Place 5-(4-formyl-2-methoxyphenoxy)pyrazine-2-carboxamide (Example 719, Part A) (0.700 g, 2.56 mmol), 3-ethylpentylamine (Example 733, Part B) (0.310 g, 2.69

mmol) and 3 Å molecular sieves in a vial. Add methanol (12.8 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.0969 g, 2.56 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 5% to 20% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate over 45 minutes. Concentrate the fraction containing the product, then add EtOAc (100mL). Wash the organic solution with 1.0 N NaOH (2 X 25 mL), dry it over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. Dissolve the product in ether:dichloromethane (5:1) (25 mL), add hexanes (20 mL), and then concentrate to about a quarter of the volume. Filter the precipitate to give the title compound (0.302 g, 31.7%): TOF MS ES<sup>+</sup> 373.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>20</sub>H<sub>29</sub>N<sub>4</sub>O<sub>3</sub> 373.2240 (M+H)<sup>+</sup>, found 373.2247, time 0.39 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 12.0 min, 100% purity.

#### Example 767

5-(4-{[2-(4-Fluorophenyl)ethylamino]methyl}-2-methoxyphenoxy)pyrazine-2-carboxamide

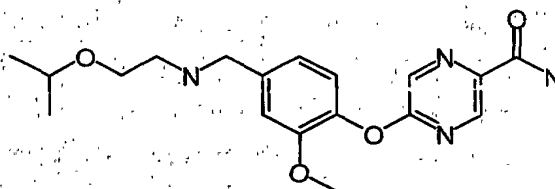


Place 5-(4-formyl-2-methoxyphenoxy)pyrazine-2-carboxamide ( Example 719, Part A) (0.700 g, 2.56 mmol), 4-fluorophenethylamine (0.374 g, 2.69 mmol) and 3 Å molecular sieves in a vial. Add methanol (12.8 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.0969 g, 2.56 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 5% to 20% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate over 45 minutes. Concentrate the fraction containing the product, then add EtOAc (100mL). Wash the organic solution with 1.0 N NaOH (2 X 25 mL), dry it over Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. Dissolve the product in ether:dichloromethane (5:1) (25 mL), add hexanes (20 mL), and then concentrate to about

a quarter of the volume. Filter the precipitate to give the title compound (0.545 g, 53.4%): TOF MS ES<sup>+</sup> 397.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>21</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>F 397.1676 (M+H)<sup>+</sup>, found 397.1689, time 0.38 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 11.2 min, 100% purity.

### Example 768

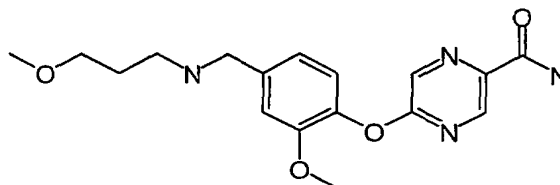
5-{4-[(2-isopropoxyethylamino)methyl]-2-methoxyphenoxy}pyrazine-2-carboxamide



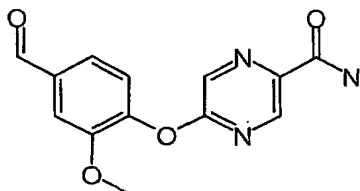
Place 5-(4-formyl-2-methoxyphenoxy)pyrazine-2-carboxamide (Example 719, Part A) (0.700 g, 2.56 mmol), 2-isopropoxyethylamine (0.278 g, 2.69 mmol) and 3 Å molecular sieves in a vial. Add methanol (12.8 mL), cap and stir overnight. Add NaBH<sub>4</sub> (0.0969 g, 2.56 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 5% to 20% (2.0 M NH<sub>3</sub> in methanol) in ethyl acetate over 45 minutes. Concentrate the fraction containing the product, then take it up in EtOAc (100mL). Wash the organic solution with 1.0 N NaOH (2 X 25 mL), dry it over Na<sub>2</sub>SO<sub>4</sub> filter and concentrate to give the title compound (0.512 g, 55.5%): TOF MS ES<sup>+</sup> 361.2 (M+H)<sup>+</sup>, HRMS calcd for C<sub>18</sub>H<sub>25</sub>N<sub>4</sub>O<sub>4</sub> 361.1876 (M+H)<sup>+</sup>, found 361.1891, time 0.38 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18], t<sub>R</sub> = 9.4 min, 100% purity.

### Example 769

## 5-{2-Methoxy-4-[(3-methoxypropylamino)methyl]phenoxy}pyrazine-2-carboxamide

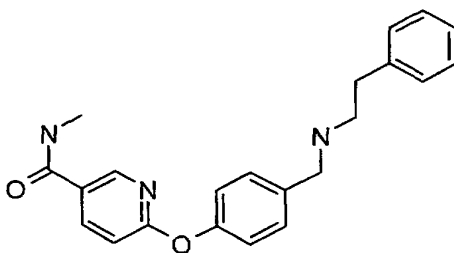
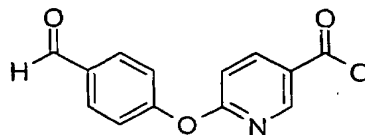


## Part A: 5-(4-Formyl-2-methoxyphenoxy)pyrazine-2-carboxamide



Dissolve 5-chloropyrazine-2-carboxamide (Example 387, Part A) (0.374 g, 2.34 mmol) and vanillin (0.361 g, 2.34 mmol) in DMF (23.7 mL). Add  $K_2CO_3$  (0.821 g, 8.94 mmol) and heat at 100 °C for 1.5 hours. Concentrate the reaction mixture. Take the solid up in water (50 mL) and extract with dichloromethane (3 X 100 mL). Dry the organic layer over  $Na_2SO_4$ , filter and concentrate to give the title compound (0.625 g, 96.4%): TOF MS  $ES^+$  274.1 (M+H) $^+$ , HRMS calcd for  $C_{13}H_{12}N_3O_4$  274.0828 (M+H) $^+$ , found 274.0829, time 0.55 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.1% TFA/acetonitrile in 0.1% TFA/water at 1.0 mL/min, 5-95 over 19 min],  $t_R$  = 10.2 min, 98.1% purity.

Part B: Place 5-(4-formyl-2-methoxyphenoxy)pyrazine-2-carboxamide (Part A) (0.700 g, 2.56 mmol), 3-methoxypropylamine (0.240 g, 2.69 mmol) and 3 Å molecular sieves in a vial. Add methanol (12.8 mL), cap and stir overnight. Add  $NaBH_4$  (0.0969 g, 2.56 mmol) and stir until the gasses stop evolving. Load the reaction mixture directly onto a 25 g ISCO<sup>®</sup> pre-load column. Dry the column in a vacuum oven at room temperature. Purify by eluting through a 40 g ISCO<sup>®</sup> column with 5% to 20% (2.0 M  $NH_3$  in methanol) in ethyl acetate over 45 minutes. Concentrate the fraction containing the product, then take it up in EtOAc (100mL). Wash the organic solution with 1.0 N NaOH (2 X 25 mL), dry it over  $Na_2SO_4$ , filter and concentrate to give the title compound (0.484 g, 54.6%): TOF MS  $ES^+$  347.2 (M+H) $^+$ , HRMS calcd for  $C_{17}H_{23}N_4O_4$  347.1719 (M+H) $^+$ , found 347.1729, time 0.38 min; HPLC [YMC-Pro pack C-18 (150 x 4.6 mm, S-5 microm), 0.05% TFA/acetonitrile in 0.05% TFA/water at 1.0 mL/min, 10-20% over 5 min, 20-95% over 18],  $t_R$  = 8.0 min, 100% purity.

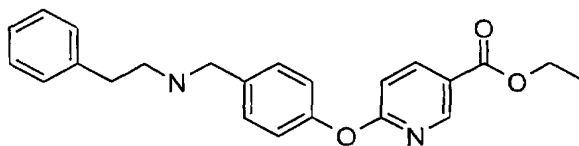
**Example 770****N-Methyl-6-[4-(phenethylamino-methyl)-phenoxy]-nicotinamide****Step 1**

Starting from 6-(4-Formyl-phenoxy)-nicotinic acid

Combine 6-(4-Formyl-phenoxy)-nicotinic acid ethyl ester (1.5 g, 5.53 mmol), MeOH (5 mL), THF (5 mL), and 5N NaOH (aq) (2mL). Reflux the reaction 18 hours and then add 1N HCl (aq) (2 mL). After concentrating the reaction on the rotovap, add Ethyl acetate to precipitate out the desired product. Filter and concentrate the ethyl acetate filtrate to afford 1.14g (85% yield) of the title compound: TLC 1:1Hexanes:Ethyl acetate  $R_f$ =0.01.

**Step 2**

6-[4-(Phenethylamino-methyl)-phenoxy]-nicotinic acid ethyl ester

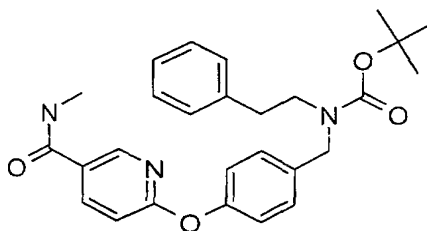


Combine 6-(4-Formyl-phenoxy)-nicotinic acid ethyl ester (0.62 g, 2.29 mmol), MeOH (12 mL), Trimethylorthoformate (8 mL), and Phenethylamine (0.26 mL, 2.06 mmol). After the reaction stirs at room temperature under a Nitrogen atmosphere for 3.5 hours, add NaBH<sub>4</sub> (251.0 mg, 2.75 mmol). After the reaction stirs at room temperature for 12 hours, concentrate under reduced pressure and add the mixture to a 5g SCX

column. Wash the column with MeOH and elute with 1N  $\text{NH}_3$  MeOH to afford 854.0 mg (99% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 2.8 (2H, t), 2.8-3.0 (4H, m), 3.8 (2H, s), 3.9 (3H, s), 6.9 (1H, d), 7.1-7.4 (9H, m), 8.3 (1H, d), 8.8 (1H, s); MS  $m/z$  377 (M+1).

### Step 3

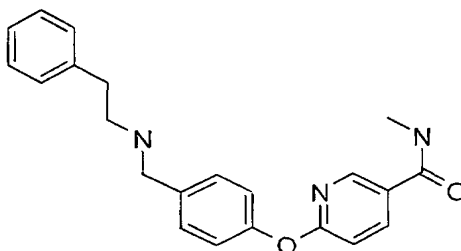
[4-(5-Ethylcarbamoyl-pyridin-2-yloxy)-benzyl]-phenethyl-carbamic acid *tert*-butyl ester



Combine 6-{4-[(*tert*-Butoxycarbonyl-phenethyl-amino)-methyl]-phenoxy}-nicotinic acid (0.097 g, 0.21 mmol),  $\text{CH}_2\text{Cl}_2$  (5 mL), EDC (0.048 g, 0.25 mmol), HOBt (0.034 g, 0.25 mmol), Hunig's Base (92  $\mu\text{L}$ , 0.53 mmol), and Methylamine Hydrochloride (0.014 g, 0.21 mmol) in a 7 mL reaction vial. After reactions shake for 72 hours, add 10% Citric acid, followed by 10%  $\text{NaHCO}_3$ , and then add the organic mixture to a Celite column. Elute with  $\text{CH}_2\text{Cl}_2$ , concentrate, and flash chromatograph using 2:1 Ethyl acetate:Hexanes eluent to afford 55.4 mg (57% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.4 (9H, s), 2.7-2.9 (2H, m), 3.0 (3H, s), 4.2-4.4 (2H, m), 4.3-4.5 (2H, m), 6.3-6.4 (1H, br s), 6.9 (1H, d), 7.0-7.4 (9H, m), 8.1 (1H, d), 8.6 (1H, s); MS  $m/z$  362 (M-100, Boc).

### Step 4

N-Methyl-6-[4-(phenethylamino-methyl)-phenoxy]-nicotinamide

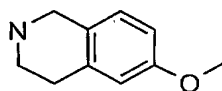


Combine [4-(5-Ethylcarbamoyl-pyridin-2-yloxy)-benzyl]-phenethyl-carbamic acid *tert*-butyl ester (55.4 mg, 0.12 mmol), CH<sub>2</sub>Cl<sub>2</sub> (4 mL), and TFA 99% (0.8 mL) in a 7 mL reaction vial. After reaction shakes on shaker at room temperature for 24 hours, concentrate under reduced pressure. Add the reaction mixture to a 2g SCX column, wash with MeOH, and elute with 1N NH<sub>3</sub> MeOH. Concentrate sample to afford 41.2 mg (95% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.5 (1H, br m), 2.7-3.0 (7H, m), 3.7 (2H, s), 6.2 (1H, br s), 6.9 (1H, d), 7.0-7.4 (9H, m), 8.0 (1H, d), 8.4 (1H, s); MS *m/z* 363 (M+1).

### Examples 771-827

#### Intermediate 1

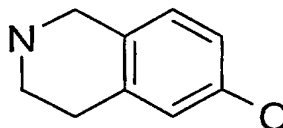
#### 6-Methoxy-1,2,3,4-tetrahydro-isoquinoline



Combine 2-(3-Methoxyphenol)ethylamine (10.0g, 66.13 mmol), 88% Formic acid, and paraformaldehyde (2.05g, 68.25 mmol) at 0°C. After the reaction stirs at room temperature for 24 hours, concentrate under reduced pressure. Add Acetyl chloride in MeOH (5ml in 80ml of MeOH) at room temperature and stir for 10 minutes. After concentration, triturate the reaction mixture with ethyl acetate, cool to room temperature, and filter to afford 8.76g, 53.7 mmol (81% yield) of the title compound as a white solid: <sup>1</sup>H NMR (500 MHz, d-MeOH); 3.05-3.15 (2H, m), 3.45-3.55 (2H, m), 3.70 (3H, s), 4.30 (2H, s), 4.8-5.0 (1H, br s), 6.8-6.9 (2H, m), 7.1-7.2 (1H, m); MS *m/z* 163 (M+).

#### Intermediate 2

#### 6-Hydroxy-1,2,3,4-tetrahydro-isoquinoline



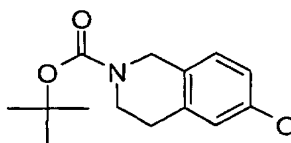
Combine 6-Methoxy-1,2,3,4-tetrahydro-isoquinoline (5.0, 20.5 mmol) and 48% HBr(aq), 20ml at room temperature. After the reaction refluxes for 24 hours, cool the reaction to room temperature and concentrate under reduced pressure. Triturate with ethyl acetate and filter to afford 5.5g, 20.5 mmol (99% yield) of the title compound as a tan solid: <sup>1</sup>H

500

NMR (500 MHz, DMSO); 2.8-2.9 (2H, m), 3.3-3.4 (2H, m), 4.1 (2H, s), 6.5-6.7 (2H, m), 6.9-7.1 (1H, m), 8.8-9.0 (2H, br s), 9.4-9.5 (1H, s).

## Intermediate 3

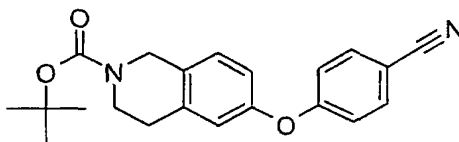
6-Hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester



Combine 6-Hydroxy-1,2,3,4-tetrahydro-isoquinoline (5.5g, 23.9 mmol), THF, 100ml, Et<sub>3</sub>N (8.3ml, 59.8 mmol), and Boc-anhydride (8.3g, 28.7 mmol). After the reaction stirs at room temperature for 72 hours under nitrogen, concentrate under reduced pressure and then flash chromatograph using 1:1 Hexanes:Ethyl acetate eluent to afford 3.51g, 14.1 mmol (59% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.5 (9H, br s), 2.7-2.8 (2H, m), 3.5-3.6 (2H, m), 4.4 (2H, s), 6.5-6.8 (2H, m), 6.9-7.0 (1H, m); MS *m/z* 150 (M<sup>+</sup>).

## Intermediate 4

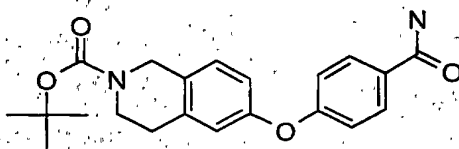
6-(4-Cyano-phenoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester



Combine in a round bottom flask equipped with a Dean Stark Trap 6-Hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (1.59g, 6.36 mmol), toluene, dimethylacetamide (10ml and 30ml respectively), K<sub>2</sub>CO<sub>3</sub> (1.25g, 9.04 mmol), and 4-Fluorobenzonitrile (0.72g, 6.04 mmol). Reflux the reaction under a Nitrogen atmosphere for 4 hours then cool to room temperature. Add water to the reaction mixture and extract the product from the water layer using ethyl acetate. The product, a white solid, precipitates out from the ethyl acetate to afford 1.93g, 5.5 mmol (87% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.5 (9H, s), 2.75-2.85 (2H, m), 3.6-3.7 (2H, m), 4.5 (2H, s), 6.8-6.9 (2H, m), 6.9-7.0 (2H, m), 7.1-7.2 (1H, m), 7.5-7.6 (2H, m); MS *m/z* 249 (M<sup>+</sup>).



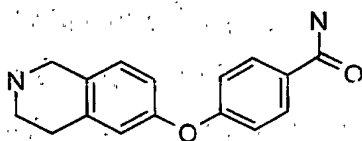
## Intermediate 5

6-(4-Carbamoyl-phenoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

Combine 6-(4-Cyano-phenoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (1.93, 5.51 mmol), *t*-butyl alcohol (50ml), and KOH (1.56g, 27.6 mmol). After the reaction stirs for 72 hours at room temperature, concentrate under reduced pressure then add ethyl acetate. Wash the ethyl acetate with a brine solution and dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>. After concentrating the organic layer under reduced pressure, the reaction affords 1.93 g, 2.50 mmol (95% yield) of the title compound as a white solid: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.5 (9H, s), 2.75-2.85 (2H, m), 3.6-3.7 (2H, m), 4.5 (2H, s), 6.8-6.9 (2H, m), 6.9-7.0 (2H, m), 7.1-7.2 (1H, m), 7.7-7.9 (2H, m); TLC R<sub>f</sub>=0.5 2:1 Hexanes:Ethyl acetate.

## Intermediate 6

4-(1,2,3,4-Tetrahydro-isoquinolin-6-yloxy)-benzamide

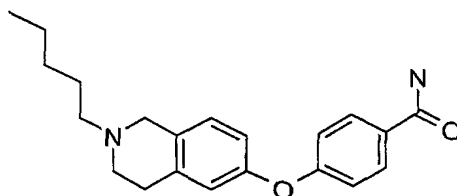


Combine 6-(4-Carbamoyl-phenoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (4.0g, 10.83 mmol), CH<sub>2</sub>Cl<sub>2</sub> (100ml), and TFA (25ml) at room temperature. After the reaction stirred for 24 hours followed by the addition of 1M K<sub>2</sub>CO<sub>3</sub> (aq), extract the product out of the aqueous layer with several washings of ethyl acetate/THF. Concentrate the organic phase under reduced pressure and add to 2, 10g SCX Columns pre-treated with 5% AcOH/MeOH. After several washings of the SCX Columns with MeOH, the elute the product using 1N NH<sub>3</sub>-MeOH solution to afford 2.08g, 7.7mmol (71% yield) of the title compound as a white foam: <sup>1</sup>H NMR (500 MHz, DMSO); 2.9-3.1 (2H, m), 3.10-3.25 (1H, m), 3.3-3.5 (2H, m), 4.1-4.3 (2H, m), 7.0-7.2

(3H, m), 7.2-7.4 (1H, m), 7.4-7.6 (1H, m), 8.0-8.1 (1H, m), 8.2-8.4 (1H, m), 8.5-8.65 (1H, m), 9.2-9.4 (2H, m); MS  $m/z$  269 (M+1).

### Example 771

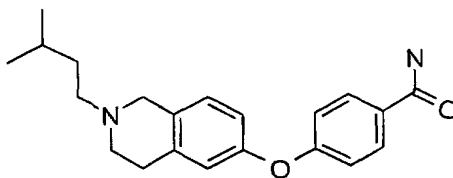
4-(2-Pentyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-benzamide



Combine 4-(1,2,3,4-Tetrahydro-isoquinolin-6-yloxy)-benzamide (80.0 mg, 0.30 mmol), DMF (4 mL),  $\text{Et}_3\text{N}$  (0.2 mL, 1.32 mmol), and Pentylbromide (0.1 mL, 0.66 mmol) in a 7 mL vial. Place vial on shaker at 70°C for 72 hours and then added Ethyl acetate to reaction vial, wash with water and several times with 10%  $\text{LiCl(aq)}$ , dry over  $\text{Na}_2\text{SO}_4$ . Concentrate the organic mixture and flash chromatograph using 2% 1N  $\text{NH}_3$  MeOH, 20% THF, 78%  $\text{CH}_2\text{Cl}_2$  to afford 78.0 mg (77% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.9-1.0 (3H, m), 1.3-1.4 (4H, m), 1.5-1.7 (2H, m), 2.4-2.6 (2H, m), 2.7-2.8 (2H, m), 2.8-3.0 (2H, m), 3.5-3.6 (2H, m), 6.8-6.8 (2H, m), 6.9-7.1 (3H, m), 7.7-7.9 (2H, m); MS  $m/z$  339 (M+1).

### Example 772

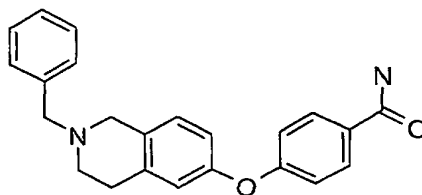
4-[2-(3-Methyl-butyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-benzamide



Using a method similar to Example 771, using Isoamylbromide (0.1 mL, 0.66 mmol) gives 63.0 mg (62% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.9-1.0 (6H, m), 1.4-1.8 (3H, m), 2.5-2.6 (2H, m), 2.7-2.8 (2H, m), 2.9-3.0 (2H, m), 3.6-3.8 (2H, m), 6.8-7.1 (5H, m), 7.7-7.9 (2H, m); MS  $m/z$  339 (M+1).

**Example 773**

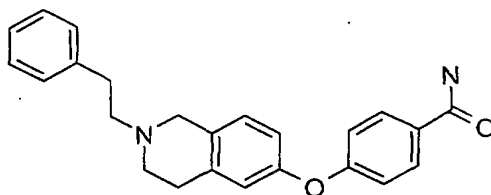
4-(2-Benzyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-benzamide



Using a method similar to Example 771, using Benzylbromide (0.1mL, 0.66 mmol) gives 81.0 mg (75% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 2.6-2.8 (2H, m), 2.8-3.0 (2H, m), 3.5-3.7 (4H, m), 5.6-6.1 (2H, br s), 6.7-6.8 (2H, m), 6.8-7.0 (3H, m), 7.2-7.4 (5H, m), 7.7-7.9 (2H, m); MS  $m/z$  359 ( $\text{M}+1$ ).

**Example 774**

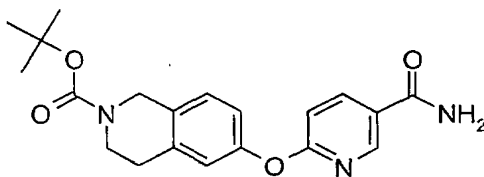
4-(5-Phenethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-benzamide



Using a method similar to Example 771, using Phenethylbromide (0.1mL, 0.66 mmol) gives 81.9 mg (73% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 2.7-3.0 (7H, m), 3.6-3.8 (3H, m), 5.8-6.2 (2H, br s), 6.8-7.1 (5H, m), 7.2-7.4 (5H, m), 7.7-7.9 (2H, m); MS  $m/z$  373 ( $\text{M}+1$ ).

**Intermediate 7**

6-(5-Carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

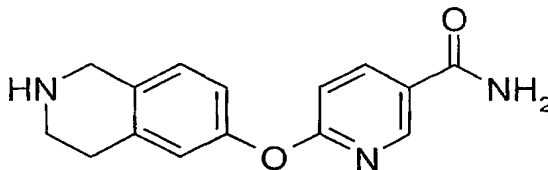


Combine in a round bottom flask equipped with a Dean Stark Trap 6-Hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (5.42g, 21.74 mmol),

Toluene, Dimethylacetamide (30ml and 90ml respectively),  $K_2CO_3$  (4.51g, 32.61 mmol), and 6-Chloronicotinamide (3.40, 21.74 mmol). Reflux the reaction under a Nitrogen atmosphere for 4 hours then cool to room temperature. Add water to the reaction mixture and extract the product from the water layer using ethyl acetate. The product, a white solid, precipitates out from the ethyl acetate to afford 5.8 g, 15.7 mmol (72% yield) of the title compound:  $^1H$  NMR (500 MHz, DMSO); 1.4 (9H, s), 2.7-2.9 (2H, m), 3.5-3.6 (2H, m), 4.4-4.6 (2H, m), 6.9-7.0 (2H, m), 7.0-7.1 (1H, m), 7.2-7.3 (1H, m), 7.5 (1H, s), 8.1 (1H, s), 8.2-8.3 (1H, m), 8.6 (1H, m).

#### Intermediate 8

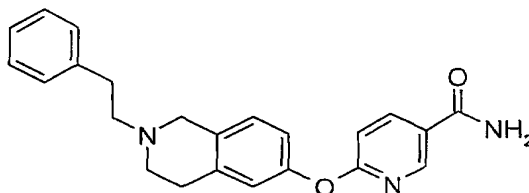
6-(1,2,3,4-Tetrahydro-isoquinolin-6-yloxy)-nicotinamide



Combine 6-(5-Carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (4.0 g, 10.83 mmol),  $CH_2Cl_2$  (100 mL), and TFA (25 mL). After reaction stirs at room temperature for 12 hours, add 1M  $K_2CO_3$  and  $CHCl_3$  to the reaction. Separate the organic layer, wash with brine, and dry over  $Na_2SO_4$ . Concentrate under reduced pressure and add mixture to 2, 10 g SCX columns, wash with MeOH, and elute with 1N  $NH_3$  MeOH. Concentrate to afford 2.91 g, 10.8 mmol (71% yield) of the title compound as a white foam:  $^1H$  NMR (500 MHz, DMSO); 2.9-3.1 (2H, m), 3.2-3.5 (2H, m), 4.2-4.4 (2H, m), 6.9-7.2 (3H, m), 7.2-7.4 (1H, m), 7.4-7.6 (1H, m), 7.9-8.1 (1H, m), 8.2-8.4 (1H, m), 8.5-8.7 (1H, m), 8.2-9.4 (2H, m); MS  $m/z$  269 (M+1).

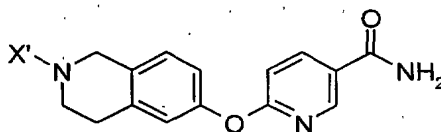
#### Example 775

6-(2-Phenethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide NF7-AOO855-011



Combine 6-(1,2,3,4-Tetrahydro-isoquinolin-6-yloxy)-nicotinamide (46.9 mg, 0.17 mmol), DMF (3 mL), Et<sub>3</sub>N (0.1 mL, 0.77 mmol), and Phenethylbromide (52  $\mu$ L, 0.38 mmol) in a 7 mL vial. Add reaction vial to a shaker at 70°C for 72 hours, and then add water and Ethyl acetate. Extract the Ethyl acetate several times with water, 10% LiCl, and dry over Na<sub>2</sub>SO<sub>4</sub>. Concentrate organic mixture and flash chromatograph using 30% THF, 4% 1N NH<sub>3</sub> MeOH, 76% CH<sub>2</sub>Cl<sub>2</sub> to afford 23.2 mg, (37% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.1-1.2 (1H, m), 1.6-2.1 (7H, m), 2.6-3.0 (9H, m), 3.6-4.0 (6H, m), 5.7-5.8 (1H, m), 6.8-7.3 (9H m), 8.0-8.2 (1H, m), 8.5-8.6 (1H, m); MS *m/z* 374(M+1).

By the method of example 775 the following compounds were prepared, isolated as the free base:



No.:	X'	Name of the Final Compound	Data
776	Benzyl	6-(2-Benzyl-1,2,3,4-tetrahydro-isoquinoline-6-yloxy)-nicotinamide	Mass spectrum (ion spray): <i>m/z</i> =360 (M+1); <sup>1</sup> H NMR (500 MHz, (CDCl <sub>3</sub> ) 2.7-3.0 (4H, m), 3.6-3.8 (4H, m), 6.8-7.1 (3H, m), 7.2-7.5 (4H, m), 8.1-8.2 (1H, m), 8.5-8.7 (1H, s).
777	Pentyl	6-(2-Pentyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide	Mass spectrum (ion spray): <i>m/z</i> =340 (M+1); <sup>1</sup> H NMR (500 MHz, (CDCl <sub>3</sub> ) 0.8-1.0 (3H, m), 1.2-1.4 (4H, m), 1.5-1.7 (2H, m), 2.4-2.6 (2H, m), 2.7-2.8 (2H, m), 2.8-3.0 (2H, m), 3.6-3.7 (2H,

				m), 5.8-6.3 (1H, br d), 6.8-7.1 (4H, m), 8.1-8.2 (1H, m), 8.5-8.7 (1H, s).
778	2-1 <i>H</i> -Indo-3-yl-ethyl	6-[2-(3-Phenyl-propyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=413$ (M+1);
779	2-(3-Chloro-benzyl)	6-[2-(3-Chloro-benzyl)-1,2,3,4-tetrahydro-isoquinoline-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=388$ (M+1);
780	2-(2-Carbamoyl-ethyl)	6-[2-(2-Carbamoyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=341$ (M+1);
781	2-(2-Phenylsulfanyl-ethyl)	6-[2-(2-Phenylsulfanyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=406$ (M+1);
782	2-(3-Methyl-butyl)	6-[2-(3-Methyl-butyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=340$ (M+1);
783	2-(4-Trifluoromethyl-benzyl)	6-[2-(4-Trifluoromethyl-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=428$ (M+1);
784	2-(3-Chloro-benzyl)	6-[2-(3-Chloro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=394$ (M+1);
785	2-(3-Phenyl-allyl)	6-[2-(3-Phenyl-allyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=386$ (M+1);
786	Benzo[b]thiopheny-3-ylmethyl	6-(2-Benzo[b]thiopheny-3-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide		Mass spectrum (ion spray): $m/z=450$ (M+1);
787	2-Cyclopropylmethyl	6-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide		Mass spectrum (ion spray): $m/z=324$ (M+1);

788	2-(3,5-Bis-trifluoromethyl-benzyl)	6-[2-(3,5-Bis-trifluoromethyl-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=496$ (M+1);
789	2-(3-Bromo-benzyl)	6-[2-(Bromo-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=438$ (M);
790	2-(4-Methyl-benzyl)	6-[2-(4-Methyl-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=374$ (M+1);
791	2-(2-Fluoro-benzyl)	6-[2-(2-Fluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=378$ (M+1);
792	2-(3-Methoxy-benzyl)	6-[2-(3-Methoxy-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=390$ (M+1);
793	2-(1H-Benzoimidazol-2-ylmethyl)	6-[2-(1H-Benzoimidazol-2-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=400$ (M+1);
794	2-(5-Chloro-thiophen-2-ylmethyl)	6-[2-(5-Chloro-thiophen-2-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=400$ (M+1);
795	2-(2,6-Dichloro-benzyl)	6-[2-(2,6-Dichloro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=428$ (M);
796	2-(3-Fluoro-benzyl)	6-[2-(3-Fluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide		Mass spectrum (ion spray): $m/z=378$ (M+1);
797	2-[2-(4-Methoxy-phenyl)-ethyl]	6-{2-[2-(4-Methoxy-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinolin-6-yloxy}-nicotinamide		Mass spectrum (ion spray): $m/z=404$ (M+1);
798	3-Propionic acid	3-[6-(5-Carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid		Mass spectrum (ion spray): $m/z=342$ (M+1);

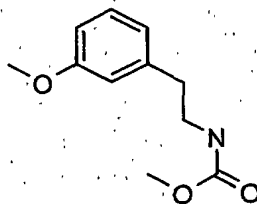
799	2-(3-Piperidin-1-yl-propyl)	6-[2-(3-Piperidin-1-yl-propyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): m/z=395 (M+1);
800	2-Pent-4-ynyl	6-(2-Pent-4-ynyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide	Mass spectrum (ion spray): m/z=336 (M+1);
801	2-(2-Piperidin-1-yl-ethyl)	6-[2-(2-Piperidin-1-yl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): m/z=381 (M+1);
802	2-(2-Diisopropylamino-ethyl)	6-[2-(2-Diisopropylamino-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): m/z=397 (M+1);
803	2-(3,3,4,4-Tetrafluoro-butyl)	6-[2-(3,3,4,4-Tetrafluoro-butyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): m/z=398 (M+1);
804	2-Cyclobutylmethyl	6-(2-Cyclobutylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide	Mass spectrum (ion spray): m/z=338 (M+1);
805	2-(3,3-Dimethyl-butyl)	6-[2-(3,3-Dimethyl-butyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): m/z=354 (M+1);
806	2-(3,4,4-Trifluoro-but-3-enyl)	6-[2-(3,4,4-Trifluoro-but-3-enyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): m/z=378 (M+1);
807	2-(2-Methoxy-benzyl)	6-[2-(2-Methoxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yloxy]-nicotinamide	Mass spectrum (ion spray): m/z=390 (M+1);
808	2-Pyridin-3-ylmethyl	6-(2-Pyridin-3-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-nicotinamide	Mass spectrum (ion spray): m/z=361 (M+1);

## Intermediate 9

[2-(3-Methoxy-phenyl)-ethyl]-carbamic acid methyl ester



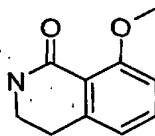
509



Combine Methoxyphenylethylamine (9.6 ml, 66.1 mmol), THF (300ml), Et<sub>3</sub>N (11.0 ml, 78.9 mmol), and methyl chloroformate (26.0 ml, 339 mmol) at 0°C under nitrogen atmosphere. After the reaction stirs at room temperature for 18 hours, add the mixture into water, wash with brine, and dry the organic layer over Na<sub>2</sub>SO<sub>4</sub> followed by concentrating under reduced pressure. Flash chromatograph using 2:1 Hexanes:Ethyl acetate to afford 13.6g, 65.0 mmol (98% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 2.8 (2H, t, J= 6.7, 7.0Hz), 3.41-3.46 (2H, m), 3.7 (3H, s), 3.8 (3H, s), 4.6-4.8 (1H, b s), 6.7-6.8 (3H, m), 7.2-7.3 (1H, m); MS *m/z* 210 (M+1).

#### Intermediate 10

8-Methoxy-3,4-dihydro-2H-isoquinolin-1-one

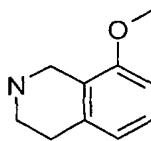


Combine polyphosphoric acid (30g) at 180°C and [2-(3-Methoxy-phenyl)-ethyl]-carbamic acid methyl ester (3.0g, 14.33 mmol). After the reaction stirs for 15 minutes then add to a beaker of ice. Extract the product from the water using CH<sub>2</sub>Cl<sub>2</sub> and CHCl<sub>3</sub>. Dry the organic layer over Na<sub>2</sub>SO<sub>4</sub> and then concentrate under reduced pressure. Flash chromatograph using 5% MeOH in Ethyl acetate to afford 0.340g, 1.92 mmol (13% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 2.92 (2H, t, J= 6.4), 3.43-3.47 (2H, m), 3.85 (3H, s), 6.2-6.3 (1H, b s), 6.8-6.9 (2H, m), 7.3-7.4 (1H, m), 7.5-7.6 (2H, m); MS *m/z* 178 (M+1).

#### Intermediate 11

8-Methoxy-1,2,3,4-tetrahydro-isoquinoline

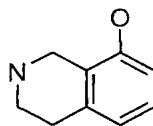
510



Combine 8-Methoxy-3,4-dihydro-2H-isoquinolin-1-one (0.778g, 4.40 mmol), THF (20ml), and  $\text{LiAlH}_4$  (0.333g, 8.8 mmol) at  $0^\circ\text{C}$  under nitrogen atmosphere. After 30 minutes the reaction, reflux for 2 hours and then cool to room temperature. Quench the reaction by adding water and 1M NaOH at  $0^\circ\text{C}$  and stirring for 12 hours at room temperature. Filter the reaction through celite and elute with THF. After concentrating the filtrate under reduced pressure, add the mixture to a 10g SCX column pre-treated with 5% AcOH/MeOH. After rinsing several times with MeOH, elute the product using 1N  $\text{NH}_3$ -MeOH followed by concentration under reduced pressure to afford 0.665g, 4.07 mmol (93% yield) of the title compound as a tan oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.7-2.0 (1H, b s), 2.77 (2H, t,  $J=5.86$ ), 3.09 (2H, t,  $J=5.86$ ), 3.8 (3H, s), 3.95 (2H, s), 6.6-6.8 (2H, m), 7.0-7.15 (1H, m); TLC 5% MeOH: Ethyl acetate  $R_f=0.1$

## Intermediate 12

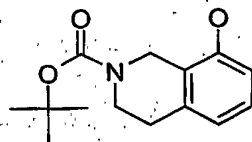
## 1,2,3,4-Tetrahydro-isoquinolin-8-ol



Combine 8-Methoxy-tetrahydroisoquinoline (665.7 mg, 4.08 mmol) and 48% HBr at room temperature. Reflux the reaction for 3 hours and then cool to room temperature. Recrystallize the product from EtOH and Diethyl ether to afford 754.2 mg, 3.28 mmol (80% yield) of the title compound as a tannish white solid:  $^1\text{H}$  NMR (500 MHz, DMSO); 2.9 (2H, t,  $J=6.16, 5.86$ ), 3.2-3.4 (2H, m), 4.0 (2H, s), 6.6-6.8 (2H, m), 7.0-7.1 (1H, m), 8.8-9.1 (2H, b m), 9.9 (1H, s); MS  $m/z$  148 ( $\text{M}^+$ ).

## Intermediate 13

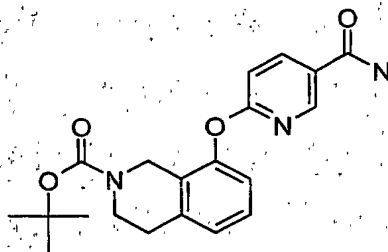
## 8-Hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester



Combine 8-Hydroxy tetrahydroisoquinoline HBr salt (754.2 mg, 3.28 mmol), and  $\text{Et}_3\text{N}$  (2.8 ml, 19.68 mmol), THF anhydrous (20 ml), and Boc-anhydride (1.14g, 3.94 mmol). Stir the reaction at room temperature for 72 hours followed by an aqueous work-up. Wash the organic layer with brine and dry over  $\text{Na}_2\text{SO}_4$ . After concentrating the organic layer under reduced pressure, flash chromatograph using 4:1 Hexanes: Ethyl acetate eluent to afford 249.6 mg, 1.01 mmol (31% yield) of the title compound as a white foam:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.5 (9H, s), 2.73-2.79 (2H, m), 3.5-3.6 (2H, m), 4.45-4.61 (2H, b s), 6.6-6.9 (2H, m), 6.9-7.2 (1H, m); TLC 4:1 Hexanes: Ethyl acetate  $R_f=0.13$

#### Intermediate 14

8-(5-Carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester



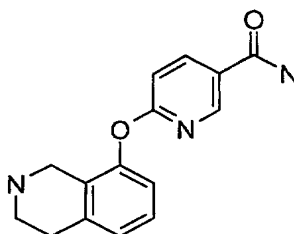
Combine in a 100 ml round bottom flask equipped with stir bar, Dean Stark trap, and reflux condenser 8-Hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (249.6 mg, 1.01 mmol), dimethylacetamide (30 ml), toluene (10 ml),  $\text{K}_2\text{CO}_3$  (814.74 mg, 5.90 mmol), and 6-Chloronicotinamide (626.28 mg, 4.0 mmol). Reflux the reaction under nitrogen for 5 hours. After cooling to room temperature, add water to the reaction mixture and extract the product using ethyl acetate. Wash the organic layer with brine and dry over  $\text{Na}_2\text{SO}_4$ . After concentrating under reduced pressure, flash chromatograph using 20% THF in  $\text{CH}_2\text{Cl}_2$  to afford 245.1mg, 0.66 mmol (66% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz, d-MeOH); 1.3-1.5 (9H, m), 2.8-2.9 (2H, m),

512

3.5-3.7 (2H, m), 3.85 (2H, s), 6.9-7.0 (1H, m), 7.1-7.2 (1H, m), 7.2-7.3 (1H, m), 7.5-7.6 (1H, m), 8.2-8.3 (1H, m), 8.6-8.7 (1H, b s), 8.8 (1H, s); MS  $m/z$  370 (M+1).

#### Intermediate 15

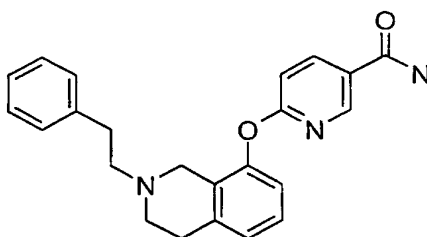
##### 6-(1,2,3,4-Tetrahydro-isoquinolin-8-yloxy)-nicotinamide



Combine 8-(5-Carbamoyl-pyridin-2-yloxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (249.6 mg, 1.01 mmol),  $\text{CH}_2\text{Cl}_2$  (25ml), and TFA (10ml) at room temperature under nitrogen atmosphere. After the reaction stirs for 12 hours then concentrate under reduced pressure. Solubilize the mixture in MeOH and add to a 2g SCX Column (pre-treated with 5% AcOH-MeOH), wash several times with MeOH, and elute the product with 1N  $\text{NH}_3$  MeOH to afford 156.1 mg, 0.58 mmol (57% yield) of the title compound.

#### Example 809

##### 6-(2-Phenethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-nicotinamide

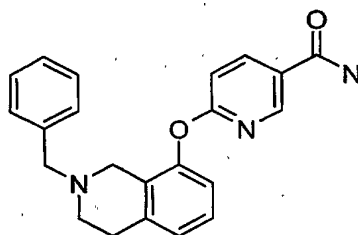


Using a method similar to Example 786, using Phenethylbromide (40  $\mu\text{L}$ , 0.28 mmol) gives 26.9 mg (55% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.8-2.1 (4H, m), 2.7-3.0 (6H, m), 5.9-6.3 (2H, br d), 6.8-7.4 (10H, m), 8.1-8.3 (1H, m), 8.5 (1H, s); MS  $m/z$  374 (M+1).

#### Example 810

##### 6-(2-Benzyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-nicotinamide

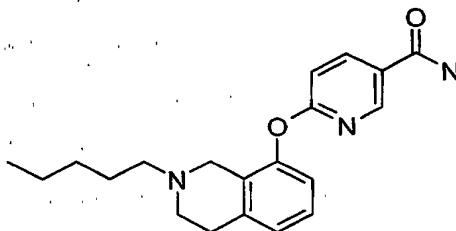
513



Using a method similar to Example 786, using Benzylbromide (0.1 mL, 0.97 mmol) gives 45.6 mg (63% yield) of the title compound.

### Example 811

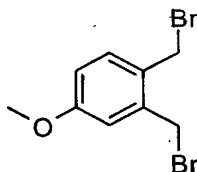
#### 6-(2-Pentyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-nicotinamide



Using a method similar to Example 786, using Pentylbromide (54  $\mu$ L, 0.48 mmol) gives 32.5 mg (48% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz, d-MeOH); 0.8 (3H, t), 1.2-1.3 (4H, m), 1.4-1.6 (2H, m), 2.3-2.5 (2H, m), 2.7 (2H, t), 2.9-3.0 (2H, m), 3.5 (2H, s), 6.8-7.2 (5H, m), 8.1-8.2 (1H, m), 8.6 (1H, s); MS  $m/z$  340 (M+1).

### Intermediate 16

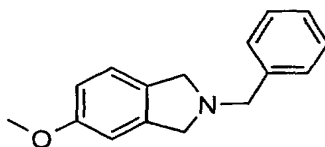
#### 1,2-Bis-bromomethyl-4-methoxy-benzene



Combine 3,4-Dimethylanisole (2.72g, 20.0mmol),  $\text{CCl}_4$  (50mL), NBS (7.12g, 40.0 mmol), and Benzoyl peroxide (40.0mg, 0.17 mmol). Reflux the reaction for 12 hours and then cool to room temperature and concentrate under reduced pressure. Flash chromatograph using 4:1  $\text{CHCl}_3$ :Hexanes eluent to afford 1.90g, 6.4 mmol (32% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 3.8 (3H, s), 4.6 (2H, s), 4.7 (2H, s), 6.8-6.9 (2H, m), 7.1-7.4 (1H, m); TLC 4:1  $\text{CHCl}_3$ :Hexanes  $R_f$ =0.67

## Intermediate 17

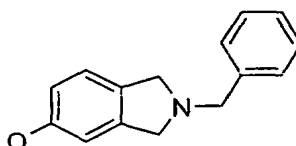
## 2-Benzyl-5-methoxy-2,3-dihydro-1H-isoindol



Combine in a round bottom flask 1,2-Bis-bromomethyl-4-methoxy-benzene (1.0g, 3.40 mmol), Benzyltriethylammonium chloride (73.5mg, 3.2 mmol), 50% NaOH(aq)/Toluene (3.0mL/14mL), and then dropwise addition of Benzylamine (0.37mL, 3.39 mmol). Stir the reaction at room temperature for 3 hours, and then add to Ethyl acetate, wash with water, brine, and dry over Na<sub>2</sub>SO<sub>4</sub>. After concentrating under reduced pressure, the add the mixture to a 10g SCX column, wash with MeOH, and elute with 1N NH<sub>3</sub>-MeOH. Flash chromatograph using 3:1 Hexanes:Ethyl acetate to afford 580.0mg, 2.42mmol (71% yield) of the title compound as a brown oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 3.7 (3H, s), 3.9-4.0 (6H, m), 6.7-6.8 (2H, m), 7.1 (1H, d), 7.3-7.5 (5H, m); MS *m/z* 238 (M).

## Intermediate 18

## 2-Benzyl-2,3-dihydro-1H-isoindol-5-ol

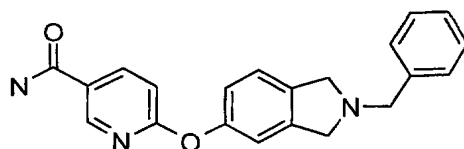


Combine 2-Benzyl-5-methoxy-2,3-dihydro-1H-isoindol (580.0mg, 2.42mmol) and 48% HBr (aq) (20mL). Reflux the reaction for 5 hours and then cool to room temperature. Concentrate the reaction mixture under reduced pressure then add to 5g a SCX column. Wash the column with MeOH and elute with 1N NH<sub>3</sub>-MeOH to afford 265.4mg, 1.17mmol (49% yield) of the title compound as a brown solid: <sup>1</sup>H NMR (500 MHz, d-Methanol); 3.8-3.9 (4H, m), 3.91 (2H, s), 6.6-6.7 (2H, m), 7.0 (1H, d), 7.2-7.5 (4H, m); MS *m/z* 226 (M+1).

## Example 812

## 6-(2-Benzyl-2,3-dihydro-1H-isoindol-5-yloxy)-nicotinamide 0

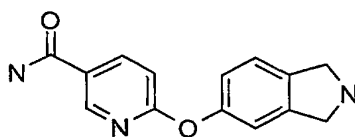
515



Combine in a round bottom flask equipped with stir, a Dean Stark Trap, and a nitrogen atmosphere 2-Benzyl-2,3-dihydro-1H-isoindol-5-ol (265.4mg, 1.18mmol), Toluene (10mL), DMA (30mL),  $K_2CO_3$  (244.6mg, 1.77mmol), and 6-Chloronicotinamide (184.4mg, 1.18mmol). Reflux the reaction for 6 hours and then cool to room temperature and add ethyl acetate. Wash the Ethyl acetate layer several times with water, brine, and dry over  $Na_2SO_4$ . After concentrating under reduced pressure, Purify the mixture by reverse phase chromatography (5% to 95% 0.01%TFA buffer in acetonitrile/water) to afford 333.4mg, 0.97mmol (82% yield) of the title compound as a white foam:  $^1H$  NMR (500 MHz, d-Methanol); 4.6-4.8 (6H, m), 7.0 (1H, d), 7.1-7.2 (2H, m), 7.4-7.6 (5H, m), 8.2 (1H, d), 8.6 (1H, s); MS  $m/z$  346 (M+1).

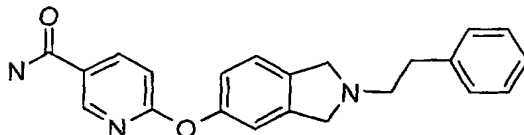
## Intermediate 19

## 6-(2,3-Dihydro-1H-isoindol-5-yloxy)-nicotinamide

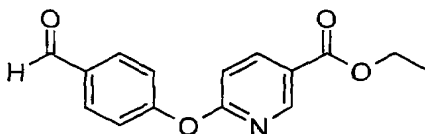


Combine 6-(2-Benzyl-2,3-dihydro-1H-isoindol-5-yloxy)-nicotinamide (230.0mg, 0.67mmol), EtOH (5mL), 10% Pd-C (45.0mg), and a Hydrogen balloon. Stir the reaction at room temperature for 168 hours at atmospheric pressure. Filter the reaction mixture through a pad of Celite using MeOH eluent and then concentrate the filtrate under reduced pressure. Add the mixture to a 2g SCX column, wash with MeOH, and elute using 1N  $NH_3$ -MeOH. After concentrating under reduced pressure, purify the mixture by flash chromatography using 10% 1N  $NH_3$ -MeOH/DCM eluent to afford 19.2 mg, 0.08mmol (11% yield) of the title compound as a white solid:  $^1H$  NMR (500 MHz, d-Methanol); 4.1-4.3 (4H, br m), 6.9-7.1 (3H, m), 7.3-7.4 (1H, m), 8.2-8.3 (1H, m), 8.6 (1H, s); MS  $m/z$  254 (M).

516

**Example 813****6-(2-Phenethyl-2,3-dihydro-1H-isoindol-5-yloxy)-nicotinamide**

Combine 6-(2,3-Dihydro-1H-isoindol-5-yloxy)-nicotinamide (19.2mg, 0.08mmol), DMF (3mL), Et<sub>3</sub>N (46 uL, 0.33mmol), and 2-Phenethylbromide (23uL, 0.165 mmol). Place the reaction on a shaker for 12 hours at 70°C, then cool to room temperature and concentrate under reduced pressure. Add the mixture to a 2g SCX column, wash with MeOH, and then elute with 1N NH<sub>3</sub>-MeOH. After concentrating the mixture, purify using reverse phase chromatography (5% to 95% 0.001% TFA buffer in acetonitrile/water) to afford 9.5mg, 0.03mmol (33% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, d-Methanol); 2.8-3.2 (4H, m), 4.1-4.2 (4H, m), 6.8-7.1 (3H, m), 7.2-7.4 (6H, m), 8.2 (1H, d), 8.6 (1H, s); MS *m/z* 358 (M).

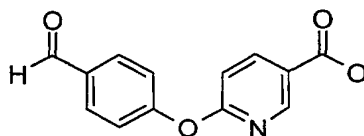
**Intermediate 20****6-(4-Formyl-phenoxy)-nicotinic acid ethyl ester**

Combine in a round bottom flask equipped with a stir, Dean Stark Trap filled with toluene, and reflux condenser 4-Hydroxybenzaldehyde (2.14 g, 17.5 mmol), K<sub>2</sub>CO<sub>3</sub> (3.63 g, 26.3 mmol), 6-Chloronicotinamide (3.25 g, 17.5 mmol) and a solution of DMA:Toluene (45:15 mL). After the reaction refluxes under nitrogen atmosphere for 3 hours, concentrate under reduced pressure and then add ethyl acetate. Wash the organic layer several times with water, then brine, and dry over Na<sub>2</sub>SO<sub>4</sub>. After concentrating under reduced pressure, flash chromatograph using 33% Hexanes, 63% Ethyl acetate eluent to afford 4.70 g, 17.4 mmol (99% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.4 (3H, t), 4.3-4.4 (2H, m), 7.1 (1H, d), 7.3-7.4 (2H, m), 7.9-8.0 (2H, m), 8.3 (1H, d), 9.9 (1H, s); TLC 2:1Hexanes:Ethyl acetate R<sub>f</sub>=0.55.

**Intermediate 21**



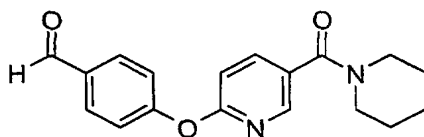
## 6-(4-Formyl-phenoxy)-nicotinic acid



Combine 6-(4-Formyl-phenoxy)-nicotinic acid ethyl ester (1.5 g, 5.53 mmol), MeOH (5 mL), THF (5 mL), and 5N NaOH (aq) (2mL). Reflux the reaction 18 hours and then add 1N HCl (aq) (2 mL). After concentrating the reaction on the rotovap, add Ethyl acetate to precipitate out the desired product. Filter and concentrate the ethyl acetate filtrate to afford 1.14g (85% yield) of the title compound: TLC 1:1Hexanes:Ethyl acetate  $R_f$ =0.01.

## Intermediate 22

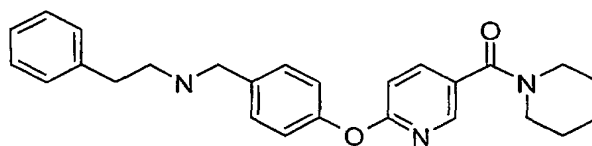
## 4-[5-(Piperidine-1-carbonyl)-pyridin-2-yloxy]-benzaldehyde



Combine 6-(4-Formyl-phenoxy)-nicotinic acid (250.0 mg, 1.03 mmol), EDC (237.0 mg, 1.23 mmol), HOBT (166.2mg, 1.23 mmol), and Piperidine (0.10 mL, 1.03 mmol) in  $\text{CH}_2\text{Cl}_2$  (6 mL). After reaction stirs at room temperature under a Nitrogen atmosphere for 24 hours, concentrate the reaction mixture using a rotovap, add Ethyl acetate and wash with 0.1N HCl, 10%  $\text{NaHCO}_3$ , Brine, and dry over  $\text{Na}_2\text{SO}_4$ . After concentrating the reaction mixture, flash chromatograph using 2:1 Ethyl acetate:Hexanes to afford 144.1 mg (45% yield) of the title compound as a white foam:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.5-1.8 (6H, m), 3.3-3.8 (4H, m), 7.0-7.1 (1H, m), 7.3-7.4 (2H, m), 7.8-8.0 (3H, m), 8.3 (1H, m), 9.9 (1H, s); MS  $m/z$  311 (M+1).

## Example 814

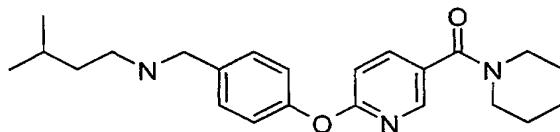
## {6-[4-(Phenethylamino-methyl)-phenoxy]-pyridin-3-yl}-piperidin-1-yl-methanone



Combine 4-[5-(Piperidine-1-carbonyl)-pyridin-2-yloxy]-benzaldehyde (72.0 mg, 0.23 mmol), MeOH (2.3 mL), Trimethylorthoformate (1.6 mL), and Phenethylamine (26  $\mu$ L, 0.21 mmol). After the reaction stirs for 72 hours at room temperature under a Nitrogen atmosphere, add NaBH<sub>4</sub> (10.5 mg, 0.28 mmol). After 5 hours, concentrate the reaction under reduced pressure and add the mixture to a 2g SCX column. Wash with MeOH and then 1N NH<sub>3</sub> MeOH to afford 72.2 mg (75% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.5-1.8 (6H, m), 2.8-3.0 (4H, m), 3.3-3.8 (4H, m), 3.85 (2H, s), 6.8 (1H, d), 7.1-7.4 (9H, m), 8.0 (1H, d), 8.2 (1H, s); MS *m/z* 416 (M+1).

### Example 815

(6-{4-[(3-Methyl-butylamino)-methyl]-phenoxy}-pyridin-3-yl)-piperidin-1-yl-

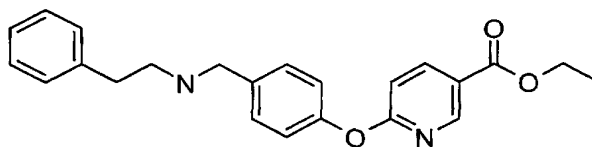


methanone

Using a method similar to Example 814, using Isoamylamine (25  $\mu$ L, 0.21 mmol) gives 63.7 mg (72% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 0.9-1.0 (6H, m), 1.3-1.4 (3H, m), 1.4-1.8 (8H, br m), 2.6 (2H, t), 3.3-3.8 (4H, br m), 3.85 (2H, s), 6.8 (1H, d), 7.1 (2H, d), 7.4 (2H, d), 7.8 (1H, d), 8.2 (1H, s); MS *m/z* 382 (M+1).

### Intermediate 23

6-[4-(Phenethylamino-methyl)-phenoxy]-nicotinic acid ethyl ester



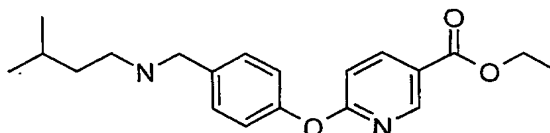
Combine 6-(4-Formyl-phenoxy)-nicotinic acid ethyl ester (0.62 g, 2.29 mmol), MeOH (12 mL), Trimethylorthoformate (8 mL), and Phenethylamine (0.26 mL, 2.06 mmol). After the reaction stirs at room temperature under a Nitrogen atmosphere for 3.5 hours, add NaBH<sub>4</sub> (251.0 mg, 2.75 mmol). After the reaction stirs at room temperature for 12 hours, concentrate under reduced pressure and add the mixture to a 5g SCX column. Wash the column with MeOH and elute with 1N NH<sub>3</sub> MeOH to afford 854.0 mg (99% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 2.8 (2H, t), 2.8-3.0 (4H,

519

m), 3.8 (2H, s), 3.9 (3H, s), 6.9 (1H, d), 7.1-7.4 (9H, m), 8.3 (1H, d), 8.8 (1H, s); MS  $m/z$  377 (M+1).

## Intermediate 24

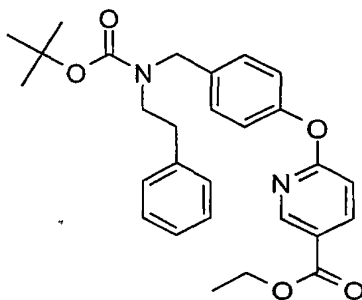
6-{4-[3-Methyl-butylamino)-methyl]-phenoxy}-nicotinic acid ethyl ester



Using a method similar to Intermediate 23, using Isoamylamine (0.20ml, 0.50 mmol) gives 854.0 mg (99% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.8-0.9 (6H, t), 1.4-1.7 (3H, m), 2.8-3.0 (2H, m), 3.8 (2H, s), 3.9 (3H, s), 6.9 (1H, d), 7.1-7.4 (4H, m), 8.3 (1H, d), 8.8 (1H, s); MS  $m/z$  343 (M+1).

## Intermediate 25

6-{4-[(*tert*-Butoxycarbonyl-phenethyl-amino)-methyl]-phenoxy}-nicotinic acid ethyl ester

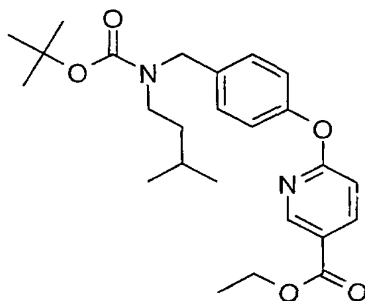


Combine 6-[4-(Phenethylamino-methyl)-phenoxy]-nicotinic acid ethyl ester (0.854 g, 2.27 mmol), THF (50 mL), Triethylamine (0.8 mL, 5.68 mmol), and Boc-anhydride (0.788 g, 2.72 mmol). After the reaction stirs at room temperature under a Nitrogen atmosphere for 2.5 hours, concentrate under reduced pressure. Add Ethyl acetate and wash with sat  $\text{NH}_4\text{Cl}$  (aq), brine, and then dry over  $\text{Na}_2\text{SO}_4$ . Concentrate the organic mixture under reduced pressure and then flash chromatograph using 8:1 to 3:1 Hexanes:Ethyl acetate gradient to afford 333.0 mg (33% yield) of title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.4 (9H, s), 2.7-2.9 (2H, m), 3.3-3.5 (2H, m), 3.9 (3H, s), 4.3-

4.4 (2H, m), 6.9 (1H, d), 7.1-7.4 (9H, m), 8.3 (1H, d), 8.8 (1H, s); MS  $m/z$  363 (M-100, Boc).

#### Intermediate 26

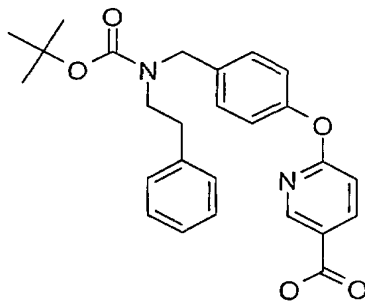
6-(4-{*tert*-Butoxycarbonyl-(3-methyl-butyl)-amino]-methyl}-phenoxy)-nicotinic acid ethyl ester



Using a method similar to Intermediate 25, using 6-{4-[3-Methyl-butylamino)-methyl]-phenoxy}-nicotinic acid ethyl ester (0.854 g, 2.27 mmol) gives 311.0 mg (31% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.8-0.9 (6H, m), 1.3-1.6 (12H, m), 3.0-3.3 (2H, m), 3.8 (3H, s), 4.2-4.4 (2H, m), 6.9 (1H, d), 7.0-7.3 (5H, m), 8.2 (1H, d), 8.7 (1H, s); TLC 3:1 Hexanes:Ethyl acetate  $R_f$ =0.34.

#### Intermediate 27

6-{4-[(*tert*-Butoxycarbonyl-phenethyl-amino)-methyl]-phenoxy}-nicotinic acid

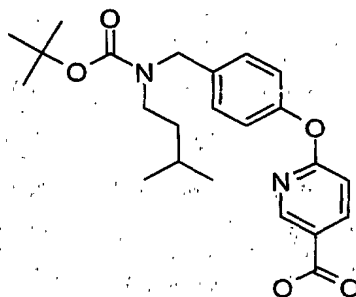


Combine 6-{4-[(*tert*-Butoxycarbonyl-phenethyl-amino)-methyl]-phenoxy}-nicotinic acid ethyl ester (0.333 g, 0.72 mmol), MeOH (5 mL), THF (5 mL), and 2.5N NaOH (aq) (2 mL). After the reaction refluxes under a Nitrogen atmosphere for 24 hours, concentrate under reduced pressure. Add 2.5N HCl (aq) (2 mL), Ethyl acetate, and wash

with water, brine, and then dry over  $\text{Na}_2\text{SO}_4$ . Concentrate the organic mixture under reduced pressure to afford 293.0 mg (91% yield) of title compound as a white foam:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.4 (9H, s), 2.6-2.8 (2H, m), 3.2-3.4 (2H, m), 4.2-4.4 (2H, m), 4.3-4.4 (2H, m), 6.9 (1H, d), 7.0-7.3 (9H, m), 8.3 (1H, d), 8.8 (1H, s); MS  $m/z$  349 (M-100, Boc).

## Intermediate 28

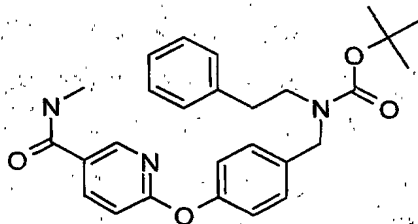
6-(4-[[*tert*-Butoxycarbonyl-(3-methyl-butyl)-amino]-methyl]-phenoxy)-nicotinic acid



Using a method similar to Intermediate 27, using 6-(4-{*tert*-Butoxycarbonyl-(3-methyl-butyl)-amino]-methyl}-phenoxy)-nicotinic acid ethyl ester (0.311 g, 0.73 mmol) gives 273.4 mg (92% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.8-0.9 (6H, m), 1.3-1.6 (12H, m), 3.0-3.3 (2H, m), 3.8 (3H, s), 4.3-4.5 (2H, m), 6.9 (1H, d), 7.0-7.4 (5H, m), 8.3 (1H, d), 8.8 (1H, s); MS  $m/z$  315 (M-100, Boc).

## Intermediate 29

[4-(5-Ethylcarbamoyl-pyridin-2-yloxy)-benzyl]-phenethyl-carbamic acid *tert*-butyl ester

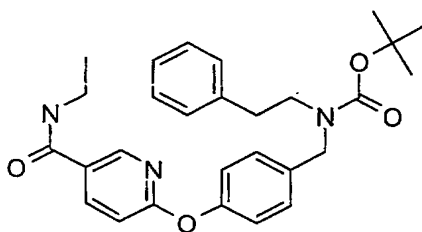


Combine 6-{4-[(*tert*-Butoxycarbonyl-phenethyl-amino)-methyl]-phenoxy}-nicotinic acid (0.097 g, 0.21 mmol),  $\text{CH}_2\text{Cl}_2$  (5 mL), EDC (0.048 g, 0.25 mmol), HOBT (0.034 g, 0.25 mmol), Hunig's Base (92  $\mu\text{L}$ , 0.53 mmol), and Methylamine Hydrochloride (0.014 g, 0.21 mmol) in a 7 mL reaction vial. After reactions shake for 72 hours, add 10% Citric

acid, followed by 10% NaHCO<sub>3</sub>, and then add the organic mixture to a Celite column. Elute with CH<sub>2</sub>Cl<sub>2</sub>, concentrate, and flash chromatograph using 2:1 Ethyl acetate:Hexanes eluent to afford 55.4 mg (57% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.4 (9H, s), 2.7-2.9 (2H, m), 3.0 (3H, s), 4.2-4.4 (2H, m), 4.3-4.5 (2H, m), 6.3-6.4 (1H, br s), 6.9 (1H, d), 7.0-7.4 (9H, m), 8.1 (1H, d), 8.6 (1H, s); MS *m/z* 362 (M-100, Boc).

## Intermediate 30

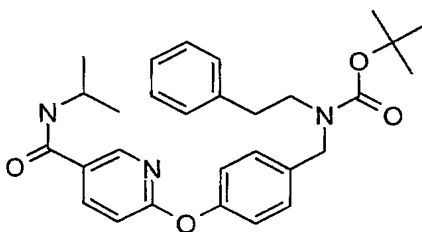
[4-(5-Ethylcarbamoyl-pyridin-2-yloxy)-phenethyl]-phenethyl-carbamic acid *tert*-butyl ester



Using a method similar to Intermediate 29, using Ethylamine, 2.0 M in MeOH (0.11 mL, 0.21 mmol) gives 72.3 mg (72% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 0.2 (3H, t), 1.4 (9H, m), 2.7-2.9 (2H, m), 3.3-3.5 (4H, m), 4.2-4.4 (2H, m), 6.2 (1H, br s), 6.9 (1H, d), 7.0-7.4 (9H, m), 8.1 (1H, d), 8.6 (1H, s); MS *m/z* 376 (M-100, Boc).

## Intermediate 31

[4-(5-Isopropylcarbamoyl-pyridin-2-yloxy)-benzyl]-phenethyl-carbamic acid *tert*-butyl ester

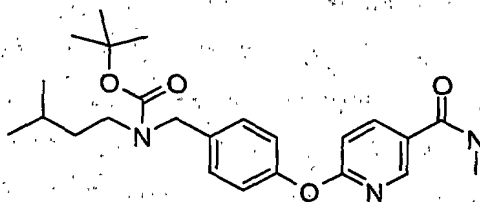


Using a method similar to Intermediate 29, using Isopropylamine, (18.0 uL, 0.21 mmol) gives 70.6 mg (69% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.2 (6H, d), 1.4 (9H, s), 2.6-2.8 (2H, m), 3.2-3.4 (2H, m), 4.2-4.4 (3H, m), 5.9 (1H, ds), 6.8 (1H, d), 6.9-7.0 (9H, m), 8.0 (1H, d), 8.4 (1H, s); MS *m/z* 390 (M-100, Boc).

523

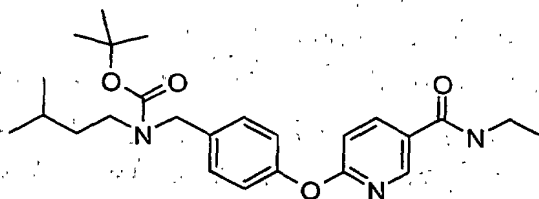
## Intermediate 32

(3-Methyl-butyl)-[4-(5-methylcarbamoyl-pyridin-2-yloxy)-benzyl]-carbamic acid *tert*-butyl ester



Combine 6-(4-[[*tert*-Butoxycarbonyl-(3-methyl-butyl)-amino]-methyl]-phenoxy)-nicotinic acid (0.090 g, 0.21 mmol), CH<sub>2</sub>Cl<sub>2</sub> (5 mL), EDC (0.048 g, 0.25 mmol), HOBt (0.034 g, 0.25 mmol), Hunig's Base (92  $\mu$ L, 0.53 mmol), and Methylamine Hydrochloride (0.014 g, 0.21 mmol) in a 7 mL reaction vial. After reactions shake for 72 hours, add 10% Citric acid, followed by 10% NaHCO<sub>3</sub>, and then add the organic mixture to a Celite column. Elute with CH<sub>2</sub>Cl<sub>2</sub>, concentrate, and flash chromatograph using 2:1 Ethyl acetate: Hexanes eluent to afford 56.2 mg (63% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 0.9 (6H, d), 1.3-1.6 (12H, m), 3.0 (3H, s), 3.1-3.3 (2H, m), 4.3-4.5 (2H, m), 6.3 (1H, br s), 6.9 (1H, d), 7.1 (2H, d), 7.2-7.4 (2H, m), 8.1 (1H, d), 8.5 (1H, s); MS *m/z* 328 (M-100, Boc).

## Intermediate 33



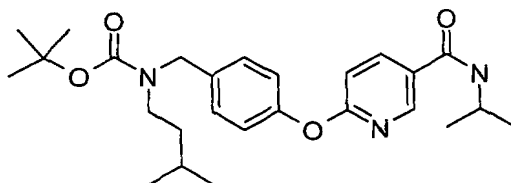
[4-(5-Ethylcarbamoyl-pyridin-2-yloxy)-benzyl]-(3-methyl-butyl)-carbamic acid *tert*-butyl ester

Using a method similar to Intermediate 42, using Ethylamine, 2.0 M in MeOH (0.11 mL, 0.21 mmol) gives 66.7 mg (72% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 0.9 (6H, d), 1.2 (3H, t), 1.3-1.6 (12H, m), 3.1-3.3 (2H, m), 3.4-3.5 (2H, m), 4.3-4.5 (2H, m), 6.2 (1H, br s), 6.9 (1H, d), 7.1 (2H, d), 7.2-7.4 (2H, m), 8.1 (1H, d), 8.5 (1H, s); MS *m/z* 328 (M-100, Boc).

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## Intermediate 34

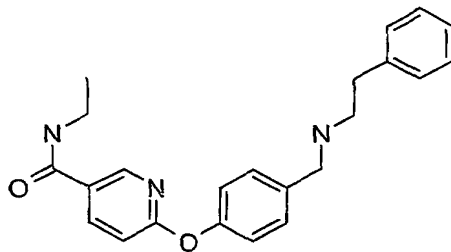
[4-(5-Isopropylcarbamoyl-pyridin-2-yloxy)-benzyl]-(3-methyl-butyl)-carbamic acid *tert*-butyl ester



Using a method similar to Intermediate 42, using Isopropylamine, (18.0  $\mu$ L, 0.21 mmol) gives 66.7 mg (41% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.9 (6H, d), 1.3 (6H, d), 1.3-1.6 (12H, m), 3.1-3.4 (2H, m), 4.2-4.3 (1H, m), 4.3-4.5 (2H, m), 5.9 (2H, br s), 6.9 (1H, d), 7.1 (2H, d), 7.2-7.4 (3H, m), 8.1 (1H, d), 8.5 (1H, s); MS  $m/z$  328 (M-100, Boc).

## Example 816

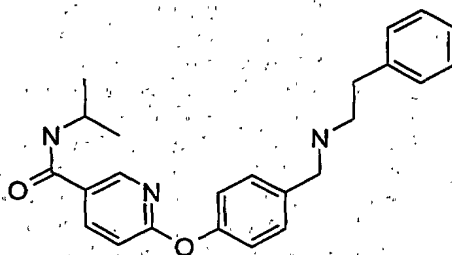
N-Ethyl-6-[4-(phenethylamino-methyl)-phenoxy]-nicotinamide



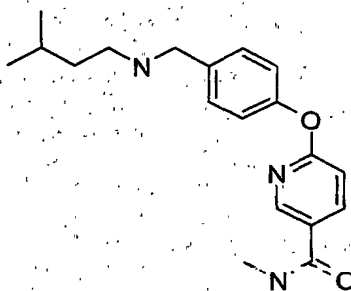
Using a method similar to Example 770, using [4-(5-Ethylcarbamoyl-pyridin-2-yloxy)]-phenethyl-carbamic acid *tert*-butyl ester (72.3 mg, 0.15 mmol) gives 45.6 mg (80% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.2 (3H, t), 2.8-3.0 (4H, m), 3.4-3.6 (2H, m), 3.8 (2H, s), 6.1 (1H, br s), 6.9 (1H, d), 7.0-7.4 (9H, m), 8.1 (1H, d), 8.5 (1H, s); MS  $m/z$  376 (M+1).

## Example 817



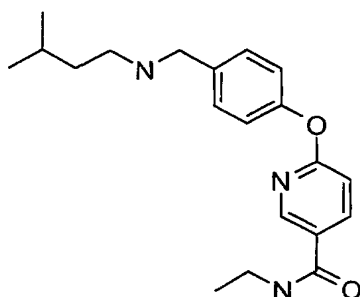
**N-Isopropyl-6-[4-(phenethylamino-methyl)-phenoxy]-nicotinamide**

Using a method similar to Example 770, using [4-(5-Isopropylcarbamoyl-pyridin-2-yloxy)-benzyl]-phenethyl-carbamic acid *tert*-butyl ester (70.6 mg, 0.14 mmol) gives 64.5 mg (99% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.3 (6H, d), 2.8-3.0 (4H, m), 3.8 (2H, s), 4.2-4.4 (1H, m), 5.9 (1H, ds), 6.9 (1H, d), 7.0-7.4 (9H, m), 8.1 (1H, d), 8.5 (1H, s); MS  $m/z$  390 (M+1).

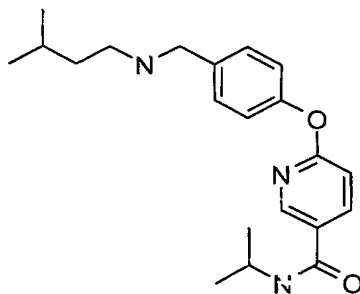
**Example 818****N-Methyl-6-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide**

Using a method similar to Example 770, using (3-Methyl-butyl)-[4-(5-methylcarbamoyl-pyridin-2-yloxy)-benzyl]-carbamic acid *tert*-butyl ester (56.2 mg, 0.13 mmol) gives 33.9 mg (79% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.9 (6H, d), 1.3-1.5 (2H, m), 1.5-1.8 (2H, br m), 2.7 (2H, t), 2.9-3.0 (4H, m), 3.8 (2H, s), 6.2 (1H, br s), 6.9 (1H, d), 7.1 (2H, d), 7.2-7.4 (2H, m), 8.1 (1H, d), 8.5 (1H, s); MS  $m/z$  328 (M+1).

**Example 819**

**N-Ethyl-6-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide**

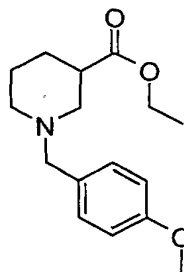
Using a method similar to Example 770, using [4-(5-Ethylcarbamoyl-pyridin-2-yloxy)-benzyl]-(3-methyl-butyl)-carbamic acid *tert*-butyl ester (66.7 mg, 0.15 mmol) gives 44.4 mg (86% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.9 (6H, d), 1.2 (3H, t), 1.3-1.5 (2H, m), 1.6-1.7 (1H, m), 2.6 (2H, t), 3.4-3.6 (2H, m), 3.8 (2H, s), 6.2 (1H, br s), 6.9 (1H, d), 7.1 (2H, d), 7.2-7.4 (2H, m), 8.1 (1H, d), 8.5 (1H, s); MS  $m/z$  342 (M+1).

**Example 820****N-Isopropyl-6-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide**

Using a method similar to Example 770, using [4-(5-Isopropylcarbamoyl-pyridin-2-yloxy)-benzyl]-(3-methyl-butyl)-carbamic acid *tert*-butyl ester (39.6 mg, 0.09 mmol) gives 26.0 mg (84% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.9 (6H, d), 1.3 (6H, d), 1.4-1.5 (2H, m), 1.5-1.7 (2H, m), 2.7 (2H, t), 3.8 (2H, s), 4.2-4.3 (1H, m), 5.9 (1H, br s), 6.9 (1H, d), 7.1 (2H, d), 7.2-7.4 (3H, m), 8.1 (1H, d), 8.5 (1H, s); MS  $m/z$  356 (M+1).

**Intermediate 35****1-(4-Methoxy-benzyl)-piperidine-3-carboxylic acid ethyl ester**

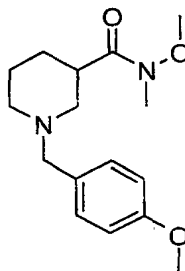
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Combine Ethyl nipecotate (9.9 mL, 63.6 mmol),  $K_2CO_3$  (13.2 g, 95.4 mmol), and DMF (300 mL) at room temperature under a Nitrogen atmosphere. Heat reaction mixture to 70°C for 30 minutes then add 4-Methoxybenzyl chloride (9.5 mL, 69.9 mmol). Stir the reaction for 5 hours at 70°C then cool the reaction mixture to room temperature and stir for an additional 12 hours. Add Ethyl acetate to the reaction mixture and extract with water and then brine. Dry the organic layer over  $Na_2SO_4$ . Concentrate under reduced pressure and flash chromatograph using 3:1 Hexanes:Ethyl acetate to give 14.6 g (82% yield) of the title compound:  $^1H$  NMR (500 MHz,  $CDCl_3$ ); 1.2 (3H, t), 1.4-1.6 (2H, m), 1.6-1.7 (1H, m), 1.9-2.1 (2H, m), 2.2 (1H, t), 1.5-1.8 (2H, m), 2.9 (1H, d), 3.5 (2H, q), 3.8 (3H, s), 4.1 (2H, dd), 6.8 (2H, d), 7.2 (2H, d); MS  $m/z$  278 (M+1).

## Intermediate 36

1-(4-Methoxy-benzyl)-piperidine-3-carboxylic acid methoxy-methyl-amide



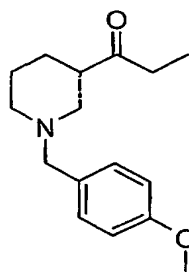
Combine 1-(4-Methoxy-benzyl)-piperidine-3-carboxylic acid ethyl ester (9.3 g, 33.5 mmol), THF (200 mL), *N,O*-Dimethylhydroxylamine hydrochloride (4.9g, 50.3 mmol) at -10°C (Acetone/ice bath) under a Nitrogen atmosphere. By dropwise addition, add Isopropylmagnesium chloride (50.3 mL, 100.6 mmol). Stir the reaction for 6 hours allowing the reaction mixture to warm to room temperature. Quench the reaction mixture with sat  $NH_4Cl$  (aq) and extract product from the water using Ethyl acetate. Wash the organic layer with brine and then dry over  $Na_2SO_4$ . Concentrate under reduced pressure

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and flash chromatograph using 1:1 Hexanes:Ethyl acetate and then 1:1 Hexanes:Ethyl acetate with 3% 1N  $\text{NH}_3$  MeOH to give 9.13 g (93% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.4-1.7 (3H, m), 1.8 (1H, d), 1.9 (1H, t), 2.1 (1H, t), 2.8-3.0 (3H, m), 3.1 (3H, s), 3.5 (2H, d), 3.6 (3H, s), 3.8 (3H, s), 6.8 (2H, d), 7.2 (2H, d); MS  $m/z$  293 (M+1).

## Intermediate 37

1-[1-(4-Methoxy-benzyl)-piperidin-3-yl]-propan-1-one NF7-AOO855-198.

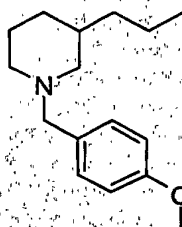


Combine 1-(4-Methoxy-benzyl)-piperidine-3-carboxylic acid methoxy-methylamide (416.0 mg, 1.42 mmol) and THF (10 mL) at  $-78^\circ\text{C}$  under a Nitrogen atmosphere. By dropwise addition, add Ethylmagnesium bromide (0.56 mL, 1.7 mmol). Stir the reaction for 12 hours allowing the reaction mixture to warm to room temperature and then add another addition of Ethylmagnesium bromide (0.56 mL, 1.7 mmol) at room temperature. After the reaction stirs for 1 hour, quench the reaction mixture with sat  $\text{NH}_4\text{Cl}$  (aq) and extract product from the water using Ethyl acetate. Wash the organic layer with brine and then dry over  $\text{Na}_2\text{SO}_4$ . Concentrate under reduced pressure and add to an SCX (5g) column pre-treated with 5% AcOH/MeOH. Wash with MeOH and elute product using 1N  $\text{NH}_3$  MeOH to give 280.6 mg (76% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz, d-MeOH); 0.9 (3H, q), 1.2-1.4 (1H, m), 1.5-1.7 (1H, m), 1.7-1.8 (1H, m), 1.9 (1H, d), 1.9-2.1 (2H, m), 2.4-2.5 (2H, m), 2.6-2.7 (1H, m), 2.8 (1H, d), 2.9 (1H, d), 3.5 (2H, s), 3.8 (3H, s), 6.8 (2H, d), 7.2 (2H, d); MS  $m/z$  262 (M+1).

## Intermediate 38

1-(4-Methoxy-benzyl)-3-propyl-piperidine

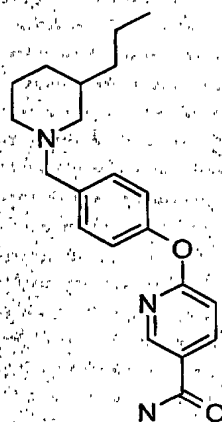
529



Combine 1-[1-(4-Methoxy-benzyl)-piperidin-3-yl]-propan-1-one (277.3 mg, 1.07 mmol), Diethylene glycol (10 mL), KOH (178.0 mg, 3.18 mmol), and Hydrazine-monohydrate (1.0 mL) at room temperature under a Nitrogen atmosphere. Heat the reaction mixture to 120°C for 2 hours and then 220°C for 4 hours. Cool reaction to room temperature and then pour the reaction mixture over sat  $\text{NH}_4\text{Cl}$  (aq). Extract with Ethyl acetate, wash with brine, and dry over  $\text{Na}_2\text{SO}_4$ . Concentrate under reduced pressure and flash chromatograph using 3% 1N  $\text{NH}_3$  MeOH in  $\text{CH}_2\text{Cl}_2$  to give 105.2 mg (40% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 0.9 (3H, t), 1.1-1.4 (4H, m), 1.5-1.7 (3H, m), 1.7 (1H, d), 1.9 (1H, td), 2.7-2.9 (2H, m), 3.5 (2H, dd), 3.8 (3H, s), 6.8 (2H, d), 7.2 (2H, d); MS  $m/z$  248 (M+1).

#### Example 821

#### 6-[4-(3-Propyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide



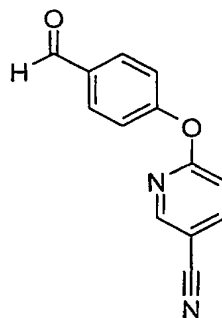
Combine 1-(4-Methoxy-benzyl)-3-propyl-piperidine (105.2 mg, 0.43 mmol), Ethanol (50 mL), 20%  $\text{Pd}(\text{OH})_2/\text{C}$  (75.0 mg), and a Hydrogen at 30°C under 50-60 psi for 12 hours on a Parr shaker. Filter the reaction mixture and then add 5% AcOH/MeOH (3 mL), 6-(4-Formyl-phenoxy)-nicotinonitrile (Intermediate 51) (40.0 mg, 0.31 mmol), and  $\text{NaCNBH}_3$  (83.7 mg, 0.34 mmol). Stir the reaction at room temperature for 72 hours and

then concentrate the reaction mixture under reduced pressure. Add the reaction mixture to an SCX Column (2g), wash with methanol, and elute with 1N NH<sub>3</sub> MeOH.

Concentrate under reduced pressure and flash chromatograph using 3% 1N NH<sub>3</sub> MeOH in CH<sub>2</sub>Cl<sub>2</sub> to give 19.8 mg (18% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 0.8-0.9 (4H, m), 1.0-1.4 (5H, m), 1.5-1.8 (4H, m), 1.9-2.1 (1H, br s), 2.8-3.0 (2H, br s), 3.4-3.7 (2H, br d), 6.9 (1H, d), 7.1(2H, d), 7.3-7.5 (2H, m), 8.1 (1H, d), 8.6 (1H, s); MS *m/z* 354 (M+1).

#### Intermediate 39

##### 6-(4-Formyl-phenoxy)-nicotinonitrile

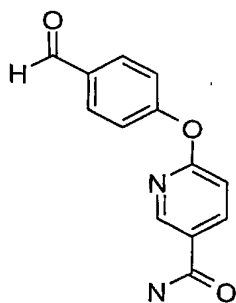


Combine 4-Hydroxybenzaldehyde (8.0 g, 65.5 mmol), 6-Chloronicotinonitrile (9.07 g, 65.5 mmol), powdered K<sub>2</sub>CO<sub>3</sub> (13.6 g, 98.3 mmol), and DMA/Toluene (80/240 mL) in a 500 mL RB flask equipped with a stir, reflux condenser, and a Dean Stark Trap. Reflux the reaction mixture for several hours under a Nitrogen atmosphere then cool to room temperature and quench with sat NH<sub>4</sub>Cl (aq). Add Ethyl acetate to extract the product and wash several times with water and then brine. Dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>. Concentrate and flash chromatograph using 2:1 Hexanes:Ethyl acetate to give 13.2 g (88% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 7.1(1H, d), 7.3-7.4 (2H, m), 7.9-8.0 (3H, m), 8.5 (1H, d), 10.0 (1H, s); MS *m/z* 225 (M+1).

#### Intermediate 40

##### 6-(4-Formyl-phenoxy)-nicotinamide

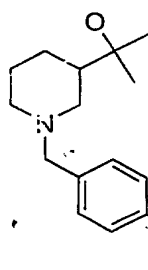
531



Combine 6-(4-Formyl-phenoxy)-nicotinonitrile (3.02 g, 13.5 mmol), powdered  $K_2CO_3$  (0.93 g, 6.7 mmol), and DMSO (100 mL) in a RB flask and add  $H_2O_2$ , 30% wt. Aq (4.05 mL, 13.5 mmol) by dropwise addition at  $0^\circ C$ . Stir the reaction mixture for 3 hours allowing it to come to room temperature then quench the reaction slowly at  $0^\circ C$  with water. Extract the product out of the water layer with ethyl acetate several times and then wash with brine. Dry over  $Na_2SO_4$  and concentrate under reduced pressure to give 2.78 g (95% yield) of the title compound:  $^1H$  NMR (500 MHz, DMSO); 7.2 (1H, d), 7.3-7.4 (2H, m), 7.5 (1H, br s), 7.9-8.0 (2H, m), 8.1 (1H, br s), 8.3 (1H, d), 8.7 (1H, s), 10.0 (1H, s); MS  $m/z$  243 (M+1).

## Intermediate 41

2-{1-(4-Methoxy-benzyl)-piperidin-3-yl}-propan-2-ol



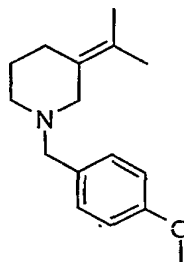
Combine 1-(4-Methoxy-benzyl)-piperidine-3-carboxylic acid ethyl ester (1.36 g, 4.9 mmol) and THF (10 mL) at  $-10^\circ C$  (Acetone/ice bath) under a Nitrogen atmosphere. By dropwise addition, add Methylmagnesium bromide (6.5 mL, 19.6 mmol). Stir the reaction for 3 hours at room temperature and then quench the reaction mixture with sat  $NH_4Cl$  (aq) and extract product from the water using Ethyl acetate. Wash the organic layer with brine and then dry over  $Na_2SO_4$ . Concentrate under reduced pressure and flash chromatograph using 3% 1N  $NH_3$ -MeOH in  $CH_2Cl_2$  to give 832.0 mg (65% yield) of the title compound:  $^1H$  NMR (500 MHz, d-MeOH); 1.1 (6H, d), 1.4-1.7 (2H, m), 1.7-

532

2.0 (4H, m), 2.8 (1H, d), 3.1 (1H, d), 3.4 (1H, s), 3.5 (2H, d), 3.8 (2H, s), 4.8 (3H, s), 6.8 (2H, d), 7.2 (2H, d); MS  $m/z$  264 (M+1).

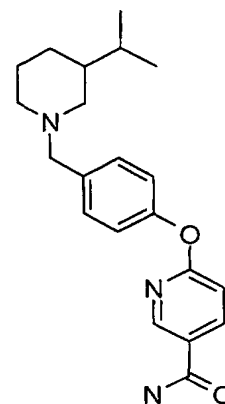
## Intermediate 42

## 3-Isopropylidene-1-(4-methoxy-benzyl)-piperidine



Combine 2-{1-(4-Methoxy-benzyl)-piperidin-3-yl}-propan-2-ol (0.564 g, 2.14 mmol) and 1:1 Et<sub>3</sub>SiH:TFA (8 mL) at room temperature. Reflux the reaction for 72 hours under a Nitrogen atmosphere and then concentrate under reduced pressure and flash chromatograph using 3% 1N NH<sub>3</sub>-MeOH in CH<sub>2</sub>Cl<sub>2</sub> to give 400.0 mg (76% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.5-1.6 (8H, d), 2.2 (2H, t), 2.5 (2H, br s), 3.0 (2H, br s), 3.5 (2H, br s), 3.8 (3H, s), 6.8 (2H, d), 7.2 (2H, d); MS  $m/z$  246 (M+1).

## Example 822



## 6-[4-(3-Isopropyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide

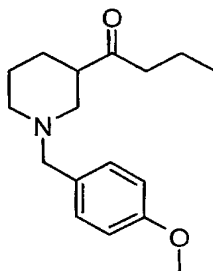
Combine 3-Isopropylidene-1-(4-methoxy-benzyl)-piperidine (227.0 mg, 0.92 mmol), Ethanol (50 mL), 20% Pd(OH)<sub>2</sub>/C (75.0 mg), and a Hydrogen at 30°C under 50-60 psi for 12 hours on a Parr shaker. Filter the reaction mixture and then add



5%AcOH/MeOH (3 mL), 6-(4-Formyl-phenoxy)-nicotinonitrile (Intermediate 51) (104.0 mg, 0.43 mmol), and NaCNBH<sub>3</sub> (49.0 mg, 0.78 mmol). Stir the reaction at room temperature for 72 hours and then concentrate the reaction mixture under reduced pressure. Add the reaction mixture to an SCX Column (2g), wash with methanol, and elute with 1N NH<sub>3</sub> MeOH. Concentrate under reduced pressure and purify by reverse phase chromatography using 5 to 95% 0.001% TFA in CH<sub>3</sub>CN/H<sub>2</sub>O to give 37.2 mg (11% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, d-MeOH); 0.9 (6H, dd), 0.9-1.1 (1H, m), 1.3-1.6 (3H, m), 1.7-1.9 (3H, m), 1.9-2.0 (1H, m), 2.9 (1H, d), 3.0 (1H, d), 3.5 (2H, dd), 6.9 (1H, d), 7.1 (2H, d), 7.4 (2H, d), 8.2 (1H, d), 8.6 (1H, s); MS *m/z* 354 (M+1).

#### Intermediate 43

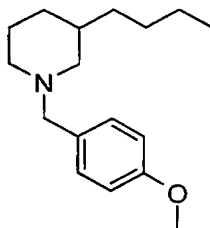
1-[1-(4-Methoxy-benzyl)-piperidin-3-yl]-butan-1-one



Combine 1-(4-Methoxy-benzyl)-piperidine-3-carboxylic acid methoxy-methylamide (401.0 mg, 1.37 mmol) and THF (10 mL) at 0°C under a Nitrogen atmosphere. By dropwise addition, add Propylmagnesium chloride (4.0 mL, 8.22 mmol). Reflux the reaction for 5 hours then cool the reaction to room temperature and quench the reaction mixture with sat NH<sub>4</sub>Cl (aq) and extract product from the water using Ethyl acetate. Wash the organic layer with brine and then dry over Na<sub>2</sub>SO<sub>4</sub>. Concentrate under reduced pressure and add to an SCX (5g) column pre-treated with 5% AcOH/MeOH. Wash with MeOH and elute product using 1N NH<sub>3</sub> MeOH to give 356.0 mg (94% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 0.8 (3H, t), 1.3 (1H, qd), 1.4-1.5 (3H, m), 1.6-1.8 (1H, m), 1.9 (1H, dd), 2.0 (1H, td), 2.1 (1H, t), 2.4 (2H, t), 2.5-2.6 (1H, m), 2.7 (1H, d), 2.9 (1H, d), 3.4 (2H, dd), 3.8 (3H, s), 6.8 (2H, d), 7.2 (2H, d); TLC 4% 1N NH<sub>3</sub> MeOH:CH<sub>2</sub>Cl<sub>2</sub> R<sub>f</sub>=0.42.

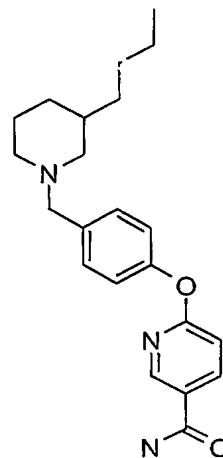
## Intermediate 44

## 3-Butyl-1-(4-methoxy-benzyl)-piperidine



Combine 1-[1-(4-Methoxy-benzyl)-piperidin-3-yl]-butan-1-one (356.0mg, 0.95 mmol), Diethylene glycol (15 mL), KOH (479.0 mg, 8.54 mmol), and Hydrazine-monohydrate (1.8 mL) at room temperature under a Nitrogen atmosphere. Heat the reaction mixture to 120°C for 2 hours and then 220°C for 24 hours. Cool reaction to room temperature and then pour the reaction mixture over sat NH<sub>4</sub>Cl (aq). Extract with Ethyl acetate, wash with brine, and dry over Na<sub>2</sub>SO<sub>4</sub>. Concentrate under reduced pressure and flash chromatograph using 3% 1N NH<sub>3</sub> MeOH in CH<sub>2</sub>Cl<sub>2</sub> to give 220.7 mg (89% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 0.7-0.9 (3H, m), 1.1-1.4 (4H, m), 1.5-1.7 (4H, m), 1.7 (1H, d), 1.9 (1H, t), 2.8 (2H, t), 3.4 (2H, dd), 3.6-3.7 (3H, m), 3.8 (3H, s), 6.8 (2H, d), 7.2 (2H, d); MS *m/z* 262 (M+1).

## Example 822



## 6-[4-(3-Butyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide

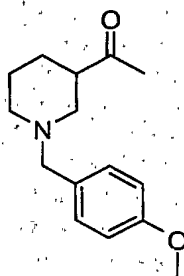
Using a method similar to Example 822, using 3-Butyl-1-(4-methoxy-benzyl)-piperidine (220.7 mg, 0.89 mmol) gives 24.6 mg (9% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 0.8-0.9 (4H, m), 1.1-1.4 (6H, m), 1.5-1.7 (4H, m), 1.8 (1H, d), 1.9 (1H, t),

535

2.9-3.0 (2H, m), 3.5 (2H, dd), 5.9-6.2 (2H, br s), 6.9 (1H, d), 7.1 (2H, d), 7.3-7.4 (2H, m), 8.2 (1H, d), 8.5 (1H, s); MS  $m/z$  368 (M+1).

## Intermediate 45

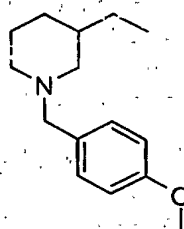
1-[1-(Methoxy-benzyl)-piperidin-3-yl]-ethanone



Using a method similar to Intermediate 43, using Methylmagnesium bromide (7.4 mL, 22.16 mmol) gives 1.37 g (73% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.4 (1H, qd), 1.5-1.6 (1H, m), 1.6-1.7 (1H, m), 1.8-1.9 (1H, m), 2.0 (1H, td), 2.1 (3H, s), 2.5-2.6 (1H, m), 2.7 (2H, d), 2.9 (1H, d), 3.5 (2H, dd), 3.8 (3H, s), 6.8 (2H, d), 7.2 (2H, d); MS  $m/z$  248 (M+1).

## Intermediate 46

3-Ethyl-1-(4-methoxy-benzyl)-piperidine

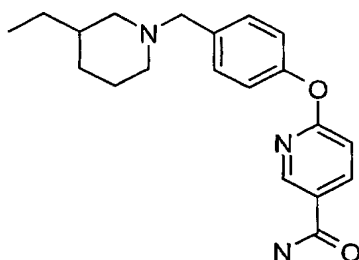


Using a method similar to Intermediate 44, using 1-[1-(Methoxy-benzyl)-piperidin-3-yl]-ethanone (1.0 g, 4.03 mmol) gives 388.3 mg (42% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.8-0.9 (4H, m), 1.1-1.2 (2H, m), 1.4-1.6 (4H, m), 1.7 (1H, d), 1.9 (1H, td), 2.8 (2H, t), 3.4 (2H, dd), 3.8 (3H, s), 6.8 (2H, d), 7.2 (2H, d); MS  $m/z$  234 (M+1).

## Example 824

6-[4-(3-Ethyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide

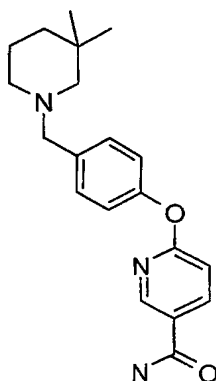
536



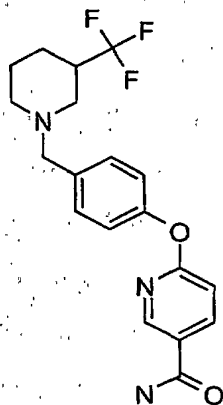
Using a method similar to Example 822, using 3-Ethyl-1-(4-methoxy-benzyl)-piperidine (388.3 mg, 1.66 mmol) gives 45.8 mg (21% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.8-0.9 (4H, m), 1.1-1.3 (2H, m), 1.4-1.6 (4H, m), 1.7 (1H, d), 1.9 (1H, t), 2.8 (2H, t), 3.5 (2H, dd), 6.0-6.2 (2H, br s), 6.9 (1H, d), 7.1 (2H, d), 7.3-7.4 (2H, m), 8.2 (1H, d), 8.5 (1H, s); MS  $m/z$  340 (M+1).

#### Example 825

##### 6-[4-(3,3-Dimethyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide



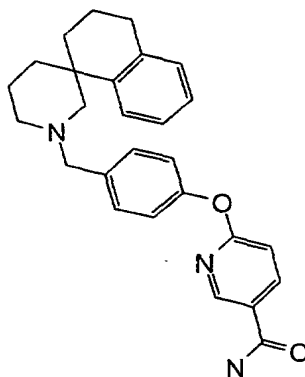
Combine 5%AcOH/MeOH (3 mL), 6-(4-Formyl-phenoxy)-nicotinonitrile (Intermediate 51) (242.24 mg, 1.0 mmol), and  $\text{NaCNBH}_3$  (113.1 mg, 1.8 mmol). Stir the reaction at room temperature for 3 hours and then concentrate the reaction mixture under reduced pressure. Add the reaction mixture to an SCX Column (2g), wash with methanol, and elute with 1N  $\text{NH}_3$  MeOH. Concentrate under reduced pressure and purify by reverse phase chromatography using 5 to 95% 0.001% TFA in  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  to give 168.0 mg (55% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.9 (6H, s), 1.2-1.3 (2H, m), 1.1.5-1.8 (4H, m), 2.0-2.1 (2H, m), 2.2-2.4 (2H, m), 3.4-3.5 (2H, m), 6.9 (1H, d), 7.1 (1H, d), 7.2 (1H, d), 7.4 (1H, d), 7.5 (1H, d), 8.2 (1H, d), 8.6 (1H, d); MS  $m/z$  340 (M+1).

**Example 826****6-[4-(3-Trifluoromethyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide**

Combine 5% AcOH/MeOH (3 mL), 6-(4-Formyl-phenoxy)-nicotinonitrile (Intermediate 51) (120.0 mg, 0.33 mmol), and NaCNBH<sub>3</sub> (184.0 mg, 0.46 mmol). Stir the reaction at room temperature for 12 hours and then concentrate the reaction mixture under reduced pressure. Add the reaction mixture to an SCX Column (2g), wash with methanol, and elute with 1N NH<sub>3</sub> MeOH. Concentrate under reduced pressure and purify by reverse phase chromatography using 5 to 95% 0.001% TFA in CH<sub>3</sub>CN/H<sub>2</sub>O to give 46.6 mg (26% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, d-MeOH); 1.2-1.4 (1H, m), 1.5-1.7 (1H, m), 1.7-1.9 (1H, m), 1.9-2.1 (2H, m), 2.3-2.5 (1H, m), 2.9 (1H, d), 3.1 (1H, d), 3.6 (2H, s), 6.9 (1H, d), 7.1 (2H, d), 7.4 (2H, d), 8.2 (1H, d), 8.6 (1H, d); MS *m/z* 380 (M+1).

**Example 827****6-[4-(3-Spiro-[1-(3,4-dihydro)naphthalene]-piperidin-1-ylmethyl)-phenoxy]-nicotinamide**

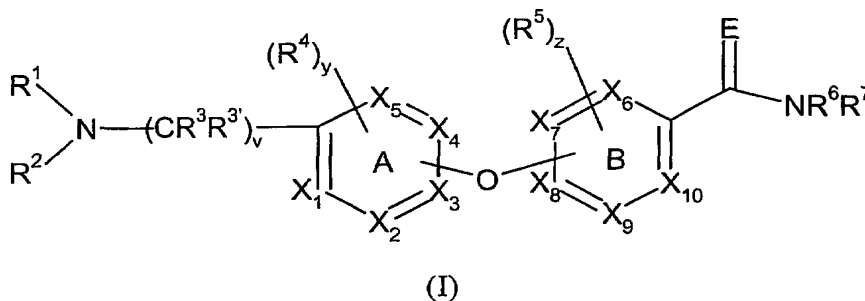
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Combine 5%AcOH/MeOH (3 mL), 6-(4-Formyl-phenoxy)-nicotinonitrile (Intermediate 51) (126.4 mg, 0.52 mmol), and NaCNBH<sub>3</sub> (65.3 mg, 1.04 mmol). Stir the reaction at room temperature for 12 hours and then concentrate the reaction mixture under reduced pressure. Add the reaction mixture to an SCX Column (2g), wash with methanol, and elute with 1N NH<sub>3</sub> MeOH. Concentrate under reduced pressure and purify by reverse phase chromatography using 5 to 95% 0.001% TFA in CH<sub>3</sub>CN/H<sub>2</sub>O to give 105.2 mg (47% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, d-MeOH); 1.5-1.8 (5H, m), 1.9-2.0 (2H, m), 2.1-2.2 (2H, m), 2.3-2.4 (1H, m), 2.5-2.8 (3H, m), 2.9 (1H, d), 3.3-3.4 (2H, m), 3.5-3.6 (1H, m), 6.9-7.2 (7H, m), 7.3-7.5 (2H, m), 8.2 (1H, d), 8.6 (1H, d); MS *m/z* 428 (M+1).

We claim:

1. A compound of formula (I)



wherein

each of  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$ ,  $X_6$ ,  $X_7$ ,  $X_8$ ,  $X_9$  and  $X_{10}$  is C, CH, or N; provided that each of rings A or B has no more than 2 nitrogen atoms;

E is O or NH;

v is 1, 2, or 3;

$R^1$  and  $R^2$  are independently selected from hydrogen,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl,  $C_2$ - $C_8$  alkynyl, aryl,  $C_3$ - $C_8$  cycloalkyl,  $-C_1$ - $C_{10}$  alkylaryl, heterocyclyl,  $-C_1$ - $C_{10}$  alkylheterocyclic, -arylheterocyclyl,  $-C_3$ - $C_8$  cycloalkylheterocyclyl,  $-C_1$ - $C_8$  alkylC(O) $C_1$ - $C_8$  alkyl, aryl C(O) $C_1$ - $C_8$  alkyl-,  $C_3$ - $C_8$  cycloalkylC(O)( $CH_2$ ) $_n$ -,  $-C_2$ - $C_8$  alkylCH(OH)aryl,  $-C_2$ - $C_8$  alkylCH(OH)cycloalkyl,  $-C_2$ - $C_8$  alkylCH(OH)heterocyclyl,  $C_2$ - $C_8$  alkylCH(OH)aryl,  $-C_1$ - $C_8$  alkylC(O)heterocyclic,  $-C_1$ - $C_8$  alkylC(O)aryl, aryloxy $C_1$ - $C_8$  alkyl-, benzhydryl, fused bicyclic,  $C_1$ - $C_8$  alkylfused bicyclic, phenylC(O)-, phenylC(O)  $C_1$ - $C_8$  alkyl-,  $C_1$ - $C_8$  alkoxy $C_1$ - $C_8$  alkyl-,  $-CO(O)C_1$ - $C_8$  alkyl,  $-SO_2C_1$ - $C_8$  alkyl,  $-SO_2C_1$ - $C_{10}$  alkylaryl,  $-SO_2C_1$ - $C_8$  alkylheterocyclic,  $-C_1$ - $C_8$  alkylcycloalkyl,  $-(CH_2)_nC(O)OR^8$ ,  $-(CH_2)_nC(O)R^8$ ,  $-(CH_2)_mC(O)NR^8R^8$ , and  $-(CH_2)_mNSO_2R^8$ ; wherein each of the alkyl, alkenyl, cycloalkyl, heterocyclic, and aryl groups are optionally substituted with one to five groups independently selected from halo,  $C_1$ - $C_8$  haloalkyl,  $C_1$ - $C_8$  thioalkyl,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl, aryl,  $-C_1$ - $C_8$  alkylaryl,  $-C(O)C_1$ - $C_8$  alkyl,  $-CO(O)C_1$ - $C_8$  alkyl,  $-SO_2C_1$ - $C_8$  alkyl,  $-SO_2C_1$ - $C_8$  alkylaryl,  $-SO_2C_1$ - $C_8$  alkylheterocyclic,  $-C_1$ - $C_8$  alkylcycloalkyl,  $-(CH_2)_nC(O)OR^8$ ,  $-(CH_2)_nC(O)R^8$ ; and wherein  $R^1$  and  $R^2$  may optionally combine with each other, or with 1, or 2 atoms adjacent to the nitrogen atom to form a 4, 5, 6, or 7-membered nitrogen-containing heterocycle which nitrogen-containing heterocycle may further have substituents selected from the group consisting of amino,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$

alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, -CO(O)C<sub>1</sub>-C<sub>8</sub> alkyl, halo, oxo, C<sub>1</sub>-C<sub>8</sub> haloalkyl; and wherein R<sup>1</sup> and R<sup>2</sup> may independently attach to the A ring to form a 4, 5, 6, or 7-member nitrogen-containing bicyclic heterocycle which nitrogen-containing bicyclic heterocycle may further have substituents selected from the group consisting of oxo, amino, -C<sub>1</sub>-C<sub>8</sub> alkyl, -C<sub>2</sub>-C<sub>8</sub> alkenyl, -C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, -CO(O)C<sub>1</sub>-C<sub>8</sub> alkyl, halo, and C<sub>1</sub>-C<sub>8</sub> haloalkyl; and wherein R<sup>1</sup> and R<sup>2</sup> are not simultaneously hydrogen; and provided that when v is 2, and R<sup>3</sup> and R<sup>3'</sup> are both hydrogen or CH<sub>3</sub>, and both A and B rings are phenyl, then the group -NR<sup>1</sup>R<sup>2</sup> is not equal to -NHCH<sub>2</sub>Phenyl; and further provided that when one of R<sup>1</sup> or R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted phenyl or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted naphthyl, or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and v is 1, and both A and B rings are phenyl, then R<sup>6</sup> and R<sup>7</sup> are not simultaneously hydrogen; R<sup>3</sup> and R<sup>3'</sup> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylcycloalkyl, and -C<sub>1</sub>-C<sub>8</sub> alkylaryl; R<sup>4</sup> and R<sup>5</sup> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, -C<sub>2</sub>-C<sub>8</sub> alkynyl, -C<sub>1</sub>-C<sub>8</sub> alkoxyalkyl, C<sub>1</sub>-C<sub>8</sub> thioalkyl, halo, C<sub>1</sub>-C<sub>8</sub> haloalkyl, -C<sub>1</sub>-C<sub>8</sub> alkoxyhaloalkyl, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, or -C(O)OC<sub>1</sub>-C<sub>8</sub> alkyl, -C<sub>1</sub>-C<sub>8</sub> alkylamino, -C<sub>1</sub>-C<sub>8</sub> alkylcycloalkyl, -(CH<sub>2</sub>)<sub>m</sub>C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, and (CH<sub>2</sub>)<sub>n</sub>NR<sup>8</sup>R<sup>8</sup>, wherein each R<sup>4</sup> or R<sup>5</sup> is attached to its respective ring only at carbon atoms, and wherein y is 0, 1, 2, or 3; and wherein z is 0, 1, 2, or 3; R<sup>6</sup> and R<sup>7</sup> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>8</sub> alkoxy, -SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub> alkyl, SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub> alkylaryl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub> alkylheterocyclic, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -C<sub>1</sub>-C<sub>6</sub> alkylcycloalkyl, -(CH<sub>2</sub>)<sub>n</sub>C(O)R<sup>8</sup>, -(CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>8</sup>R<sup>8</sup>, and -(CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>R<sup>8</sup>; wherein each of the alkyl, alkenyl, and aryl groups are optionally substituted with one to five groups independently selected from C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, aryl, and C<sub>1</sub>-C<sub>8</sub> alkylaryl; and wherein R<sup>6</sup> and R<sup>7</sup> may independently combine with each other, and with the nitrogen atom to which they are attached or with 1, or 2 atoms adjacent to the nitrogen atom to form a 4, 5, 6, or 7-membered nitrogen containing heterocycle which nitrogen containing heterocycle may optionally have substituents selected from the group consisting of oxo, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, -



CO(O)C<sub>1</sub>-C<sub>8</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>8</sub> alkoxy, -C<sub>1</sub>-C<sub>8</sub> alkylamine, amino, halo, and haloalkyl;

R<sup>8</sup> is hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, or -C(O)OC<sub>1</sub>-C<sub>8</sub> alkyl; and wherein n is 0, 1, 2, 3 or 4 and m is 1, 2, or 3;

or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof.

2. The compound according to claim 1 wherein the A-ring is selected from the group consisting of phenyl, pyridine, pyrimidine, pyrazine, and pyridazine.

3. A compound according to Claim 1 wherein the B-ring is selected from the group consisting of phenyl, pyridine, pyrimidine, pyrazine, and pyridazine.

4. A compound according to Claim 1 wherein the A-ring is phenyl and the B ring is pyridinyl.

5. A compound according to Claim 1 wherein the A ring is phenyl and the B ring is pyrazinyl.

6. A compound according to Claim 1 wherein the A-ring is pyridinyl and the B-ring is phenyl.

7. A compound according to Claim 1 wherein both rings A and B are pyridinyl.

8. A compound according to Claim 1 wherein both rings A and B are phenyl.

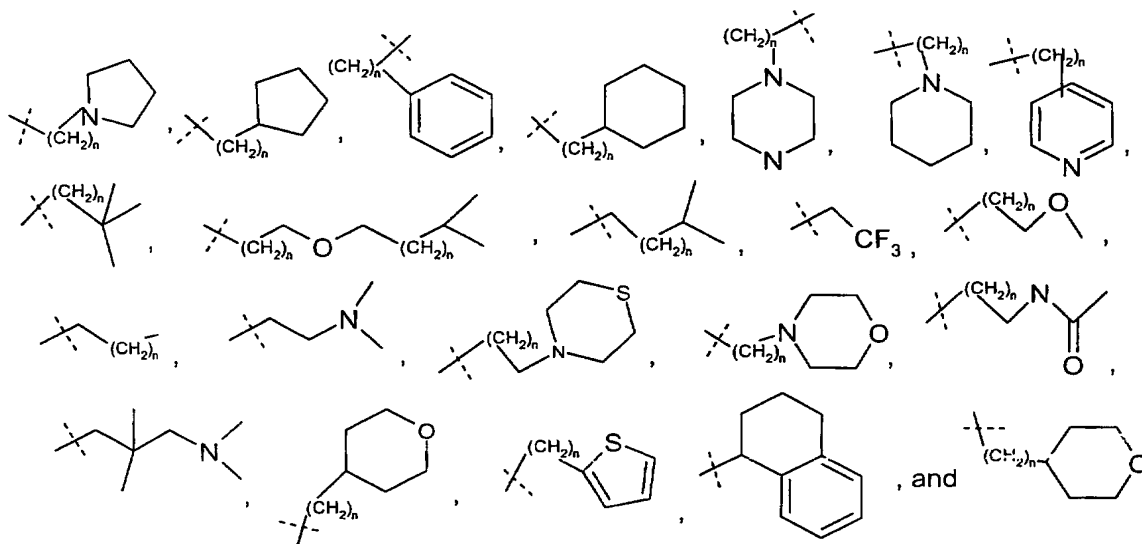
9. A compound according to any one of Claims 1 to 8 wherein E is an oxygen atom.

10. A compound according to Claim 1 wherein y is 0, 1, or 2, and R<sup>4</sup> is independently selected from the group consisting of hydrogen, fluoro, chloro, bromo.

methoxy, ethoxy, methyl, ethyl, isopropyl, trifluoromethyl, trifluoromethoxy, phenyl, and benzyl.

11. A compound according to Claim 1 wherein  $z$  is 0, 1, or 2, and  $R^5$  is independently selected from the group consisting of hydrogen, fluoro, chloro, bromo, methoxy, ethoxy, methyl, ethyl, isopropyl, trifluoromethyl, trifluoromethoxy, phenyl, and benzyl.

12. A compound according to Claim 1 wherein  $R^1$  and  $R^2$  are each independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, phenyl,



and wherein  $n$  is 1, 2, or 3.

13. The compound according to any one of Claims 1 to 12 wherein  $R^6$  and  $R^7$  are each independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, phenyl, provided that when one of  $R^1$  or  $R^2$  is  $-\text{CH}_2\text{CH}_2$ -optionally substituted phenyl or  $-\text{CH}_2\text{CH}_2$ -optionally substituted naphthyl, or  $-\text{CH}_2\text{CH}_2$ -optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and  $v$  is 1, and the B ring is phenyl, then  $R^6$  and  $R^7$  are not simultaneously hydrogen.

14. A compound according to any one of Claims 1 to 12 wherein E is an oxygen atom, R<sup>6</sup> and R<sup>7</sup> are each hydrogen provided that R<sup>1</sup> and R<sup>2</sup> are not simultaneously hydrogen and further provided that when one of R<sup>1</sup> or R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted phenyl or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted naphthyl, or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and v is 1, the B ring is not phenyl.

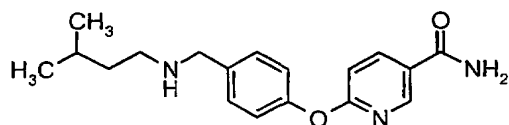
15. A compound according to any one of Claims 1 to 12 wherein v is 1 or 2.

16. A compound according to any one of Claims 1 to 12 wherein v is 1.

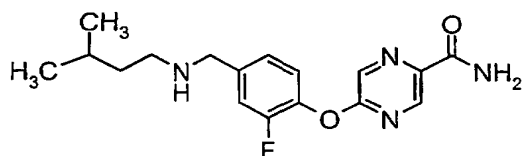
17. A compound according to any one of Claims 1 to 12 wherein vis 2, m is 1, n is 1, y is 0 or 1 and z is 0 or 1.

18. A compound selected from the group consisting of:

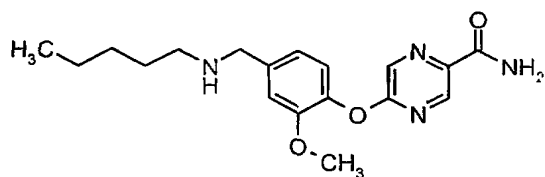
6-{4-[(3-Methyl-butylamino)-methyl]-phenoxy}-nicotinamide



5-{2-Fluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-pyrazine-2-carboxamide

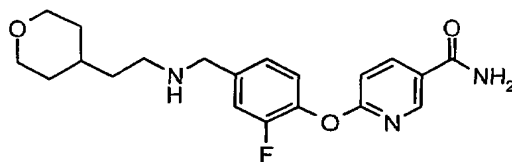


5-(2-Methoxy-4-pentylaminomethyl-phenoxy)-pyrazine-2-carboxamide

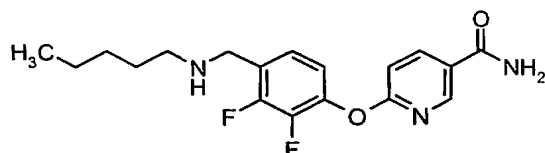


6-(2-Fluoro-4-{[2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl}-phenoxy)-nicotinamide

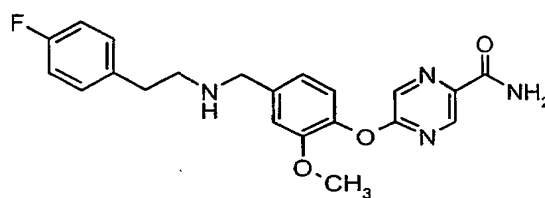
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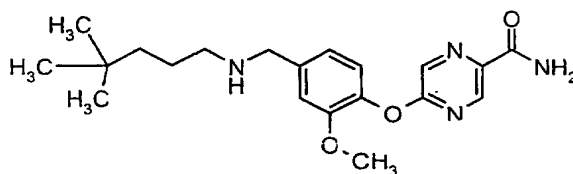
6-(2,3-Difluoro-4-pentylaminomethyl-phenoxy)-nicotinamide



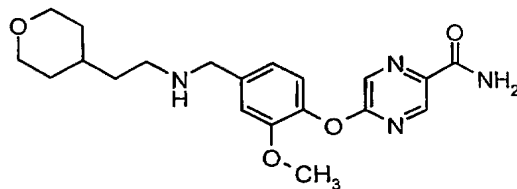
5-(4-{[2-(4-Fluoro-phenyl)-ethylamino]-methyl}-2-methoxy-phenoxy)-pyrazine-2-carboxamide



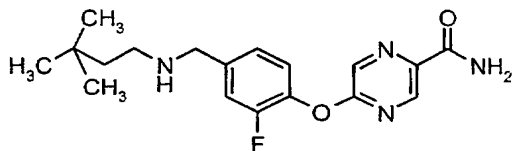
5-{4-[(4,4-Dimethyl-pentylamino)-methyl]-2-methoxy-phenoxy}-pyrazine-2-carboxamide



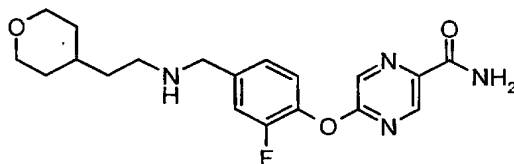
5-(2-Methoxy-4-{[2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl}-phenoxy)-pyrazine-2-carboxamide



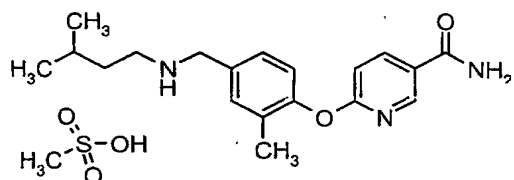
5-{4-[(3,3-Dimethyl-butylamino)-methyl]-2-fluoro-phenoxy}-pyrazine-2-carboxamide



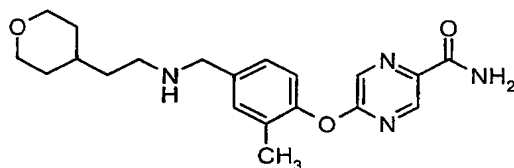
5-(2-Fluoro-4-{{2-(tetrahydro-pyran-4-yl)-ethylamino}-methyl}-phenoxy)-pyrazine-2-carboxamide



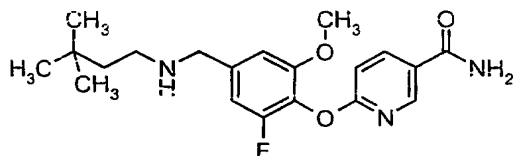
6-{2-Methyl-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide; methanesulfonic acid salt



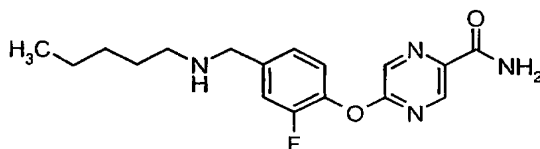
5-(2-Methyl-4-{{2-(tetrahydro-pyran-4-yl)-ethylamino}-methyl}-phenoxy)-pyrazine-2-carboxamide



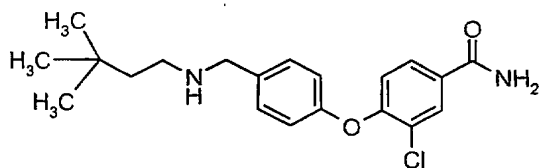
6-{4-[(3,3-Dimethyl-butylamino)-methyl]-2-fluoro-6-methoxy-phenoxy}-nicotinamide



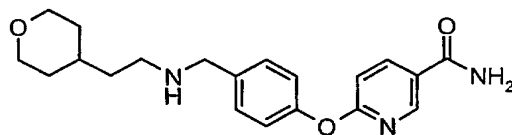
5-(2-Fluoro-4-pentylaminomethyl-phenoxy)-pyrazine-2-carboxamide



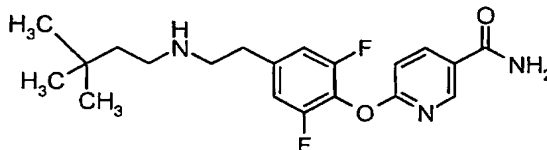
3-Chloro-4-{4-[(3,3-dimethyl-butylamino)-methyl]-phenoxy}-benzamide



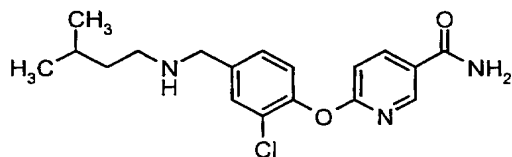
6-(4-{[2-(Tetrahydro-pyran-4-yl)-ethylamino]-methyl}-phenoxy)-nicotinamide



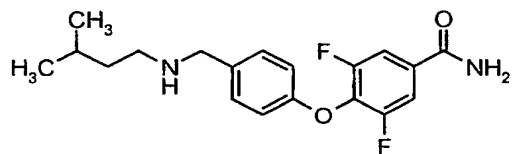
6-{4-[2-(3,3-Dimethyl-butylamino)-ethyl]-2,6-difluoro-phenoxy}-nicotinamide



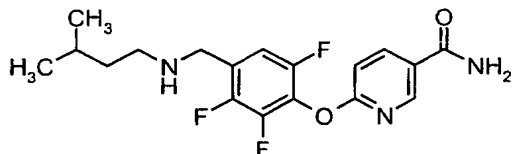
6-{2-Chloro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide



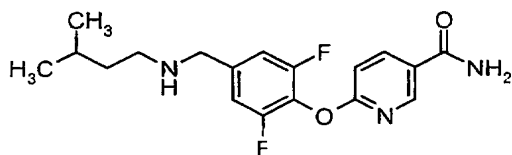
3,5-Difluoro-4-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide



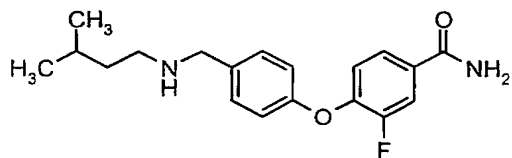
6-{2,3,6-Trifluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide



6-{2,6-Difluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide

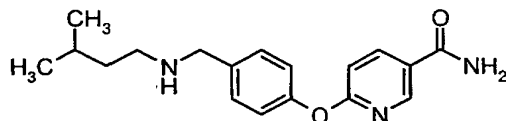


3-Fluoro-4-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide



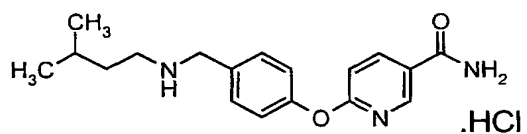
and a pharmaceutically acceptable salt, or solvate thereof.

19. The compound 6-{4-[(3-Methyl-butylamino)-methyl]-phenoxy}-nicotinamide

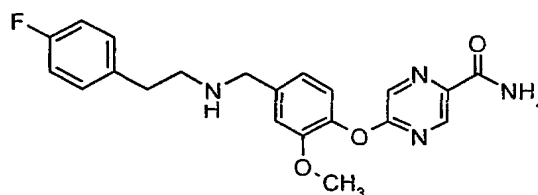


or a pharmaceutically acceptable salt, or solvate thereof.

20. The hydrochloric acid salt of the compound 6-{4-[(3-Methyl-butylamino)-methyl]-phenoxy}-nicotinamide

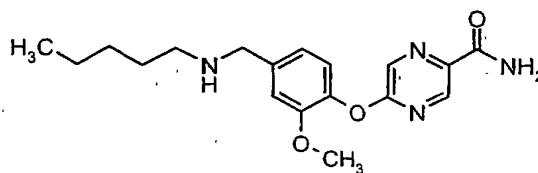


21. The compound 5-(4-{[2-(4-Fluoro-phenyl)-ethylamino]-methyl}-2-methoxy-phenoxy)-pyrazine-2-carboxamide



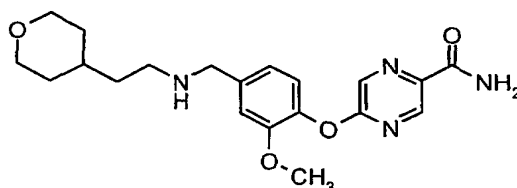
or a pharmaceutically acceptable salt, or solvate thereof.

22. The compound 5-(2-Methoxy-4-pentylaminomethyl-phenoxy)-pyrazine-2-carboxylic acid amide



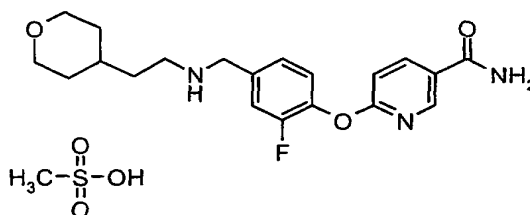
or a pharmaceutically acceptable salt, or solvate thereof.

23. The compound 5-(2-Methoxy-4-{{2-(tetrahydro-pyran-4-yl)-ethylamino}-methyl}-phenoxy)-pyrazine-2-carboxamide



or a pharmaceutically acceptable salt, or solvate thereof.

24. The compound 6-(2-Fluoro-4-{{2-(tetrahydro-pyran-4-yl)-ethylamino}-methyl}-phenoxy)-nicotinamide; methanesulfonic acid salt



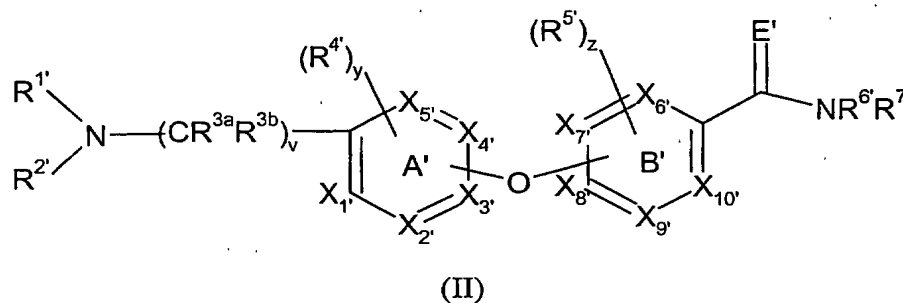
25. A compound according to any one of Claims 1 to 18 wherein the pharmaceutically acceptable salt is the hydrochloric acid salt, the methanesulfonic acid salt, hydrobromide salt, the bisulfate salt or tartaric acid salt.

26. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of Claims 1 to 24 in association with a carrier, diluent and/or excipient.

27. A method for blocking a mu, kappa, delta or receptor combination (heterodimer) thereof in mammals comprising administering to a mammal requiring blocking of a mu, kappa, delta or receptor combination (heterodimer) thereof, a receptor blocking dose of a compound according to any one of Claims 1 to 24, or a pharmaceutically acceptable salt, enantiomer, racemate, mixture of diastereomers, or solvate thereof.



28. A method of treating or preventing obesity and Related Diseases comprising administering a therapeutically effective amount of a compound of formula II wherein formula II is represented by the structure



wherein

each of  $X_1'$ ,  $X_2'$ ,  $X_3'$ ,  $X_4'$ ,  $X_5'$ ,  $X_6'$ ,  $X_7'$ ,  $X_8'$ ,  $X_9'$  and  $X_{10}'$  is C, CH, or N; provided that each of rings A' or B' has no more than 2 nitrogen atoms;

$E'$  is O or NH;

$v$  is 0, 1, 2 or 3;

$R^{1'}$  and  $R^{2'}$  are independently selected from hydrogen,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl,  $C_2$ - $C_8$  alkynyl, aryl,  $C_3$ - $C_8$  cycloalkyl,  $-C_1$ - $C_{10}$  alkylaryl, heterocyclyl,  $-C_1$ - $C_{10}$  alkylheterocyclic, -arylheterocyclyl,  $-C_3$ - $C_8$  cycloalkylheterocyclyl,  $-C_1$ - $C_8$  alkylC(O) $C_1$ - $C_8$  alkyl, aryl C(O) $C_1$ - $C_8$  alkyl-,  $C_3$ - $C_8$  cycloalkylC(O)( $CH_2$ ) $n$ -,  $-C_2$ - $C_8$  alkylCH(OH)aryl,  $-C_2$ - $C_8$  alkylCH(OH)cycloalkyl,  $-C_2$ - $C_8$  alkylCH(OH)heterocyclyl  $C_2$ - $C_8$  alkylCH(OH)aryl,  $-C_1$ - $C_8$  alkylC(O)heterocyclic,  $-C_1$ - $C_8$  alkylC(O)aryl, aryloxy $C_1$ - $C_8$  alkyl-, benzhydryl, fused bicyclic,  $C_1$ - $C_8$  alkylfused bicyclic, phenylC(O)-, phenylC(O)  $C_1$ - $C_8$  alkyl-,  $C_1$ - $C_8$  alkoxy $C_1$ - $C_8$  alkyl-,  $-CO(O)C_1$ - $C_8$ alkyl,  $-SO_2C_1$ - $C_8$ alkyl,  $-SO_2C_1$ - $C_{10}$  alkylaryl,  $-SO_2C_1$ - $C_8$  alkylheterocyclic,  $-C_1$ - $C_8$  alkylcycloalkyl,  $-(CH_2)_nC(O)OR^8$ ,  $-(CH_2)_nC(O)R^8$ ,  $-(CH_2)_mC(O)NR^8R^8$ , and  $-(CH_2)_mNSO_2R^8$ ; wherein each of the alkyl, alkenyl, cycloalkyl, heterocyclic, and aryl groups are optionally substituted with one to five groups independently selected from halo,  $C_1$ - $C_8$  haloalkyl,  $C_1$ - $C_8$  thioalkyl,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl, aryl,  $-C_1$ - $C_8$  alkylaryl,  $-C(O)C_1$ - $C_8$  alkyl,  $-CO(O)C_1$ - $C_8$  alkyl,  $-SO_2C_1$ - $C_8$  alkyl,  $-SO_2C_1$ - $C_8$  alkylaryl,  $-SO_2C_1$ - $C_8$  alkylheterocyclic,  $-C_1$ - $C_8$  alkylcycloalkyl,  $-(CH_2)_nC(O)OR^8$ ,  $-(CH_2)_nC(O)R^8$ ; and wherein  $R^{1'}$  and  $R^{2'}$  may optionally combine with each other, or with 1, or 2 atoms adjacent to the nitrogen atom to form a 4, 5, 6, or 7-membered nitrogen-containing heterocycle which nitrogen-containing heterocycle may further have substituents selected from the group consisting of amino,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$

alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, -CO(O)C<sub>1</sub>-C<sub>8</sub> alkyl, halo, oxo, C<sub>1</sub>-C<sub>8</sub> haloalkyl; and wherein R<sup>1'</sup> and R<sup>2'</sup> may independently attach to the A' ring to form a 4, 5, 6, or 7-member nitrogen-containing bicyclic heterocycle which nitrogen-containing bicyclic heterocycle may further have substituents selected from the group consisting of oxo, amino, -C<sub>1</sub>-C<sub>8</sub> alkyl, -C<sub>2</sub>-C<sub>8</sub> alkenyl, -C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, -CO(O)C<sub>1</sub>-C<sub>8</sub> alkyl, halo, and C<sub>1</sub>-C<sub>8</sub> haloalkyl; provided that R<sup>1'</sup> and R<sup>2'</sup> are not simultaneously hydrogen; and provided that when v is 2, and R<sup>3a</sup> and R<sup>3b</sup> are both hydrogen or CH<sub>3</sub>, and both A' and B' rings are phenyl, then the group -NR<sup>1'</sup>R<sup>2'</sup> is not equal to -NHCH<sub>2</sub>Phenyl; and further provided that when one of R<sup>1'</sup> or R<sup>2'</sup> is -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted phenyl or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted naphthyl, or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and v is 1, and both A' and B' rings are phenyl, then R<sup>6'</sup> and R<sup>7'</sup> are not simultaneously hydrogen;

R<sup>3a</sup> and R<sup>3b</sup> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylcycloalkyl, aryl, and -C<sub>1</sub>-C<sub>8</sub> alkylaryl;

R<sup>4'</sup> and R<sup>5'</sup> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, -C<sub>2</sub>-C<sub>8</sub> alkynyl, -C<sub>1</sub>-C<sub>8</sub> alkoxyalkyl, C<sub>1</sub>-C<sub>8</sub> thioalkyl, halo, C<sub>1</sub>-C<sub>8</sub> haloalkyl, -C<sub>1</sub>-C<sub>8</sub> alkoxyhaloalkyl, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, or -C(O)OC<sub>1</sub>-C<sub>8</sub> alkyl, -C<sub>1</sub>-C<sub>8</sub> alkylamino, -C<sub>1</sub>-C<sub>8</sub> alkylcycloalkyl, -(CH<sub>2</sub>)<sub>m</sub>C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, and -(CH<sub>2</sub>)<sub>n</sub>NR<sup>8</sup>R<sup>8</sup>, wherein each R<sup>4'</sup> and R<sup>5'</sup> is attached to its respective ring only at carbon atoms, and wherein y is 0, 1, 2, or 3; and wherein z is 0, 1, 2, or 3;

R<sup>6'</sup> and R<sup>7'</sup> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>8</sub> alkoxy, -SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub> alkyl, SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub> alkylaryl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub> alkylheterocyclic, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -C<sub>1</sub>-C<sub>6</sub> alkylcycloalkyl, -(CH<sub>2</sub>)<sub>n</sub>C(O)R<sup>8</sup>, -(CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>8</sup>R<sup>8</sup>, and -(CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>R<sup>8</sup>; wherein each of the alkyl, alkenyl, and aryl groups are optionally substituted with one to five groups independently selected from C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, aryl, and C<sub>1</sub>-C<sub>8</sub> alkylaryl; and wherein R<sup>6'</sup> and R<sup>7'</sup> may independently combine together, and with the nitrogen atom to which they are attached or with 1, or 2 atoms adjacent to the nitrogen atom to form a 4, 5, 6, or 7-membered nitrogen containing heterocycle which nitrogen containing heterocycle may further have substituents selected from the group consisting of C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub>

alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, phenyl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, -CO(O)C<sub>1</sub>-C<sub>8</sub> alkyl, hydroxy, -C<sub>1</sub>-C<sub>8</sub> alkoxy, halo, and haloalkyl;

R<sup>8</sup> is hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, or -C(O)OC<sub>1</sub>-C<sub>8</sub> alkyl; wherein n is 0, 1, 2, 3 or 4 and wherein m is 1, 2 or 3;

or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomers or mixtures thereof.

29. A method according to Claim 28 wherein the Related Diseases is selected from the group consisting of diabetes, diabetic complications, diabetic retinopathy, atherosclerosis, hyperlipidemia, hypertriglyceridemia, hyperglycemia, and hyperlipoproteinemia.

30. A method of treating and/or preventing diseases related to obesity including irritable bowel syndrome, nausea, vomiting, obesity-related depression, obesity-related anxiety, smoking and alcohol addiction, sexual dysfunction, substance abuse, drug overdose, addictive behavior disorders, compulsive behaviors and stroke, comprising administering a therapeutically effective amount of a compound of formula I or II.

31. Use of a compound of formula I according to any one of Claims 1 to 24 or a compound of formula II according to Claim 28 in the manufacture of a medicament for the treatment and/or amelioration of the symptoms associated with obesity and Related Diseases.

32. A method of treating and/or preventing obesity and Related Diseases comprising administering a therapeutically effective amount of a compound of formula I or II to a patient in need thereof.

33. A method of suppressing appetite in a patient in need thereof, comprising administering a therapeutically effective amount of a compound of formula I or II.

34. A method of effecting weight loss in an obese patient comprising administering an effective amount of a compound of formula I or formula II or pharmaceutically acceptable salt, solvate, racemate or enantiomer thereof.

35. Use of a compound according to Claim 18 for the treatment of obesity comprising administering an effective dose of said compound to a person in need thereof.

36. Use of a compound according to Claim 18 for the treatment of weight loss comprising administering an effective dose of said compound to a person in need thereof.

37. Use of a compound according to Claim 19 or 20 or 21 or 22 or 23 or 24 for the treatment of obesity comprising administering an effective dose of said compound to a person in need thereof.

38. A pharmaceutical composition for the treatment and/or amelioration of the symptoms associated with obesity and Related Diseases, containing as an active ingredient a compound of formula I according to any one of Claims 1 to 24 or a compound of formula II according to Claim 28.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/26300

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4412 C07D213/82 C07D401/12 C07D241/24 C07D401/06  
 C07D333/20 A61K31/4427 A61P3/04 C07C43/20

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 827 746 A (LILLY CO ELI) 11 March 1998 (1998-03-11) preparation 93, compounds of formula XIIIX-page 15 and formula XXIII-page 16 claims	1-38
X	WO 97 10825 A (LILLY CO ELI ;BELL MICHAEL G (US); CROWELL THOMAS A (US); DROSTE C) 27 March 1997 (1997-03-27) page 7; claims	1-38
X	WO 02 06276 A (SCHOTTEN THEO ;EVERS BRITTA (DE); RUEHTER GERD (DE); STENZEL WOLFG) 24 January 2002 (2002-01-24) page 74, line 16 -page 82, line 18; claims; tables 3,6,7 page 13, line 1-7,15-20	1-38
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

19 February 2004

Date of mailing of the international search report

27/02/2004

Name and mailing address of the ISA

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Authorized officer

Gavriliu, D

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/26300

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 921 120 A (LILLY CO ELI) 9 June 1999 (1999-06-09) claims page 7 page 8 page 14	1-38
A	US 4 891 379 A (ZIMMERMAN DENNIS M ET AL) 2 January 1990 (1990-01-02) cited in the application column 22, line 62 -column 32, line 3; claims	1-38
A	US 6 436 959 B1 (FITZPATRICK LOUIS J ET AL) 20 August 2002 (2002-08-20) column 16, line 60 -column 18, line 65; claims; examples	1-38
A	WO 99 67204 A (DELORME DANIEL ;ROBERTS EDWARD (CA); ASTRA PHARMA INC (CA); ASTRA) 29 December 1999 (1999-12-29) page 49, line 1 -page 53, line 25; claims	1-38
A	WO 00 40560 A (ISHIKAWA HIROHUMI ;TANIGUCHI KIYOSHI (JP); WASHIZUKA KENICHI (JP);) 13 July 2000 (2000-07-13) page 14, line 6 -page 16, line 11; claims; examples 2,11,12	1-38

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present Claim 1 relates to an extremely large number of possible compounds. In fact, Claim 1 contains so many options, variables, possible permutations that a lack of clarity (and conciseness) within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT arises to such an extent as to render a meaningful search of the Claim 1 impossible. The Claim 1 can in no way be considered to be a reasonable generalisation of the actual examples since it include numerous possibilities which cannot be considered as equivalents, homologues or analogues of the tested examples. Consequently, the search was carried out for those parts of the application which do appear to be clear (concise and supported by the examples), namely for the compounds of formula Ib (as defined in the description page 547). It is pointed out that all the compounds claimed by the present Claims 18-24 as well as all the tested compounds fall under general structure Ib.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/26300

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 27-30, 32-37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/26300

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0827746	A	11-03-1998	AT 215369 T 15-04-2002
		AU 4094197 A 26-03-1998	
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